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(54) Title: NOVEL PLEXINS AND USES THEREOF

(57) Abstract: The invention provides methods and compositions related to novel plexins. The polypeptides may be produced recombinantly from transformed host cells and from the disclosed plexin encoding nucleic acids or purified from human cells. The invention provides isolated plexin hybridization probes and primers capable of specifically hybridizing with the disclosed plexin genes, plexin-specific binding agents such as specific antibodies, and methods of making and using the subject compositions in diagnosis, therapy and in biopharmaceutical industry. The invention also provides novel plexin neuropilin multimeric receptor complexes for semaphorins and methods of use thereof, including but not limited to, the treatment and diagnosis of neurological disease and neuroregeneration, immune modulation, and viral and oncological diseases.

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NOVEL PLEXINS AND USES THEREOF

BACKGROUND OF THE INVENTION

Field of the Invention

5 The invention relates to the identification and characterization of four novel proteins that are members of the plexin family.

Summary of the Related Art

Plexin family members encode large transmembrane proteins, whose cysteine-rich extracellular domains share regions of homology with the Scatter Factor receptors (encoded by the Met gene family). The extracellular domains of plexins also contain
10 ~500 amino acid Semaphorin domains (see below). The highly conserved cytoplasmic moieties of plexins (approx. 600 amino acids), however, have no homology with the Met tyrosine kinase domain, nor with any other known protein. Met-like receptors and their ligands, the Scatter Factors, mediate a complex biological program including
15 dissociation of cell-cell contacts, motility and invasion (for a review see Tamagnone, L. and Comoglio, P.M. (1997) "Control of invasive growth by hepatocyte growth factor (HGF) and related scatter factors." Cytokine Growth Factor Rev 8, 129-142). During embryogenesis Scatter Factor-1 and Met promote the dissociation of cell layers in the somites and drive the migration of myogenic cells to their appropriate location (Bladt, F., Riethmacher, D., Isenmann, S., Aguzzi, A., and Birchmeier, C. (1995) "Essential
20 role for the c-met receptor in the migration of myogenic precursor cells into the limb bud." Nature 376, 768-771; Maina, F., Casagrande, F., Audero, E., Simeone, A., Comoglio, P.M., Klein, R.a., and Ponzetto, C. (1996) "Uncoupling of grb2 from the met receptor in vivo reveals complex roles in muscle development." Cell 87, 531-542).
25 Met and Scatter Factor-1 are also involved in controlling neurite outgrowth and axonal guidance (Ebens, A., Brose, K., Leonardo, E.D., Hanson, M.G.J., Bladt, F., Birchmeier, C., Barres, B.A., and Tessier-Lavigne, M. (1996) "Hepatocyte growth factor/scatter factor is an axonal chemoattractant and a neurotrophic factor for spinal motor neurons." Neuron 17, 1157-1172; Maina, F., Hilton, M.C., Ponzetto, C., Davies, A.M., and
30 Klein, R. (1997) "Met receptor signaling is required for sensory nerve development and HGF promotes axonal growth and survival of sensory neurons." Genes Dev 11, 3341-3350; Maina, F., Hilton, M.C., Andres, R., Wyatt, S., Klein, R., and Davies, A.M.

(1998) "Multiple roles for hepatocyte growth factor in sympathetic neuron development." *Neuron* 20, 835-846).

The first clue regarding a possible function for plexins came from the finding that a novel plexin, Vespr, interacts with the viral semaphorin A39R (Comeau, M.R., Johnson, R., DuBose, R.F., Petersen, M., Gearing, P., VandenBos, T., Park, L., Farrah, T., Buller, R.M., Cohen, J.I., Strockbine, L.D., Rauch, C., and Spriggs, M.K. (1998) "A poxvirus-encoded semaphorin induces cytokine production from monocytes and binds to a novel cellular semaphorin receptor, VESPR." *Immunity*. 8, 473-482). Semaphorins are a large family of secreted and membrane-bound molecules that are characterized by an extracellular domain containing a ~500 amino acid Semaphorin domain (Kolodkin et al. (1993) "The semaphorin genes encode a family of transmembrane and secreted growth cone guidance molecules." *Cell* 75, 1389-1399). As noted above, plexins contain a more divergent but nevertheless conserved Semaphorin domain.

Semaphorins were originally characterized in the nervous system, where they have been implicated in repulsive axon guidance (Kolodkin et al. (1993) *supra*; Luo, Y., Raible, D., and Raper, J.A. (1993) "Collapsin: a protein in brain that induces the collapse and paralysis of neuronal growth cones." *Cell* 75, 217-227; Tessier-Lavigne, M. and Goodman, C.S. (1996) "The molecular biology of axon guidance." *Science* 274, 1123-1133). More recently, semaphorins have been furthermore implicated in cardiac and skeletal development (Behar, O., Golden, J.A., Mashimo, H., Schoen, F.J., and Fishman, M.C. (1996) "Semaphorin III is needed for normal patterning and growth of nerves, bones and heart." *Nature* 383, 525-528), in the immune response (Hall, K.T., Boumsell, L., Schultze, J.L., Boussiotis, V.A., Dorfman, D.M., Cardoso, A.A., Bensussan, A., Nadler, L.M., and Freeman, G.J. (1996) "Human CD100, a novel leukocyte semaphorin that promotes B-cell aggregation and differentiation." *Proc.Natl.Acad.Sci.U.S.A.* 93, 11780-11785), in the regulation of angiogenesis (Miao, H.Q., Soker, S., Feiner, L., Alonso, J.L., Raper, J.A., and Klagsbrun, M. (1999) "Neuropilin-1 mediates collapsin-1/Semaphorin III inhibition of endothelial cell motility. Functional competition of collapsin-1 and vascular endothelial growth factor-165" [In Process Citation]. *J Cell Biol* 146, 233-242), and in tumor growth and metastasis (Christensen, C.R., Klingelhofer, J., Tarabykina, S., Hulgaard, E.F., Kramerov, D., and Lukanidin, E. (1998) "Transcription of a novel mouse semaphorin

gene, M-semaH, correlates with the metastatic ability of mouse tumor cell lines." Cancer Res. 58, 1238-1244).

Previously identified plexins have been shown to be expressed in the developing nervous system, (i.e. Plexin-A is a receptor for class 1 semaphorins (Sema-1a and Sema-1b). Moreover, Plexin-A has been shown via genetic analysis to control motor and CNS axon guidance induced by semaphorins (Winberg, M.L., Noordermeer, J.N., Tamagnone, L., Comoglio, P.M., Spriggs, M.K., Tessier-Lavigne, M., and Goodman, C.S. (1998). Plexin A is a neuronal semaphorin receptor that controls axon guidance. Cell 95, 903-916).

Thus a need exists for discovery of other members of the plexin family of proteins.

SUMMARY OF THE INVENTION

The present invention provides four novel plexin family members.

In one aspect, the invention provides an isolated nucleic acid having at least 80% nucleic acid sequence identity to a nucleotide sequence that encodes an amino acid sequence selected from the group consisting of the amino acid sequence shown in (SEQ ID NO: 2), (SEQ ID NO: 4), (SEQ ID NO: 6) and (SEQ ID NO: 8).

In other aspects, the invention provides isolated nucleic acid having at least 80% nucleic acid sequence identity to a nucleotide sequence selected from the group consisting of the nucleotide sequence shown in (SEQ ID NO: 1), (SEQ ID NO: 3), (SEQ ID NO: 5) and (SEQ ID NO: 7).

In another aspect, the invention provides a vector comprising the nucleic acid of the above-aspects.

The invention also provides an isolated polypeptide the amino acid sequence of which comprises residues 1-18, 19-518, 451-530, 601-680, 751-830, 800-1010, or 1196-1215 of SEQ ID NO: 2; 1-23, 24-507 or 1100-1119 of SEQ ID NO: 4; or 1-42, 43-600, 541-620, 691-770, 831-910, 900-1110 or 1270-1293 of SEQ ID NO: 6; or 8-49, 154-199 or 1-199 of SEQ ID NO: 8.

In another aspect, the invention provides an isolated polypeptide having at least 80% amino acid sequence identity to an amino acid sequence selected from the group consisting of the amino acid sequence shown in (SEQ ID NO: 2), (SEQ ID NO: 4), (SEQ ID NO: 6) and (SEQ ID NO: 8)

The invention also provides a chimeric molecule comprising a polypeptide of the above aspects fused to a heterologous amino acid sequence. In one embodiment the heterologous amino acid sequence is a Fc region of an immunoglobulin.

In other aspects, the invention provides an antibody that specifically
5 binds to the polypeptides of the above aspects.

The invention also provides a method of treating, suppressing or altering a disorder involving aberrant immune regulation involving a signaling pathway between a plexin and a neuropilin in a mammal comprising the step of administering an effective amount of an agent to said mammal capable of interfering with the association between
10 the plexin and neuropilin. Contemplated agents include a chimeric molecule or an antibody of the above aspects.

DESCRIPTION OF THE DRAWINGS

Figure 1.

(A) Phylogenetic tree of human plexins. Known family members cluster in two
15 major groups: plexin A and plexin-B subfamilies. (B) Structural features of plexins, Met-like receptors and semaphorins. In the extracellular moieties, yellow boxes indicate the "sema" domains and blue boxes mark the cysteine-rich MRS motifs, some of which are stippled to indicate their atypical sequence; atypical MRS are also found in the *sema domain* of semaphorins. Sequence identity among *sema* domains ranges from 15-50%,
20 as previously described (see Winberg et al., 1998 *supra*). Potential furin-like proteolytic sites are marked by red ribbons. plexin-B1 "truncated" is the product of a splicing variant (see text). plexin-D1 and plexin-C1 (VESPR) are more distant family members, since they include atypical features in their extracellular domains. The intracellular domain of plexins (SP domain) is highly conserved through all family
25 members, and it includes two separate regions of high homology (Maestrini, E., Tamagnone, T., Longati, P., Cremona, O., Gulisano, M., Bione, S., Tamanini, F., Neel, B.G., Toniolo, D., and Comoglio, P.M. (1996) "A family of transmembrane proteins with homology to the MET-hepatocyte growth factor receptor." Proc. Natl. Acad. Sci. USA 93, 674-678) (green oval and box). Met-like receptors are disulfide-bound
30 heterodimers and include a cytoplasmic tyrosine kinase domain (red box). Mammalian semaphorins can be either secreted or cell surface proteins. Molecular weights of representative proteins are Plexin-A1 220 kDa, Plexin-B1 250 kDa, Plexin-C1 200

kDa, HGF-R/Met 145+45 kDa (heterodimer), Sema 4D 150 kDa (transmembrane), Sema7A approx. 100 kDa (membrane GPI-linked).

Figure 2.

(a) Cell surface semaphorins specifically bind human plexins. Micrographs of the binding assays done testing i) the extracellular domain of semaphorin CD100 fused to alkaline phosphatase (CD100-AP) on COS cells transfected with *plexin-B1 cDNA*; ii) control AP on plexin-B1; iii) CD100-AP on plexin-B2; iv) CD100-AP on the entire extracellular domain of plexin-B1; v) CD100-AP on isolated "plexin-B1 truncated" (including *sema* domain, 1° and 2° MRS); vi) CD100-AP on a "plexin-B1- Δ sema" (including 2° and 3° MRS; -vii) extracellular domain of semaphorin A39R fused to AP, on plexin-C1 (Vespr); viii) SemaK1-AP on plexin-C1. The final detection of the binding was done either using alkaline phosphatase substrates (i-vi) or by immunofluorescence (vii and viii). (B) Scatchard analysis and binding curve of CD100-AP to plexin-B1 ($K_D = 0.9 \text{ nM} \pm 0.15$).

Figure 3.

Plexins associate with neuropilins *via* specific extracellular domains. Western blots of immunoprecipitated samples from cells co-expressing neuropilins and plexins. Specific MoAbs were used, directed against the VSV-tag included in plexins or the myc-tag included in neuropilin-2 (Np2, 130 kDa). Np2 co-immunoprecipitates with plexins, such as plexin-A3 (220 kDa), the extracellular domain of plexinA1 (approx. 160 kDa), and plexin-B1 (250 kDa) but not with the unrelated cell surface receptor DCC (170 kDa). Np2 can also associate a truncated form of the extracellular moiety of plexin-B1 ("plex-B1 trunc.", approx. 110 kDa), containing the *sema domain*.

Figure 4.

Expression of mRNAs for plexins A1 (panel A, B), -A2 (panel C, D) and A3 (panel E, F) in the spinal cord (sc), dorsal root ganglia (d) and sympathetic ganglia (sg) of E13.5 mouse embryos. Expression of the mRNAs was detected by RNA in situ hybridization. Scale bar: 1 μm .

Figure 5.

Effect of a truncated plexin-A1 construct (lacking the cytoplasmic domain) on repulsive and attractive responses of *Xenopus* spinal neurons to Sema3A and netrin-1. (A-F) A control spinal neuron exposed to a gradient of Sema3A emanating from a pipette (A) is repelled away over a period of 1 hr (B). In contrast, a GFP-expressing

spinal neuron from an embryo injected with mRNA for the truncated plexin-A1 construct (C) is not affected by Sema3A (D). A similar neuron (E) shows a normal attractive response to netrin-1 (F).

(G) Cumulative distribution plot of turning angles for all the neurons studied. Curves show the percent of neurons with turning angles less than the angle indicated on the abscissa, under different conditions (open circles, control neurons; black and blue circles, control neurons responding to Sema3A or netrin-1, respectively; red and green circles, responses of neurons expressing the truncated plexin-A1 construct to Sema3A and netrin-1, respectively. (H) Mean turning angle under all the conditions just mentioned.

Figure 6.

Tyrosine phosphorylation of plexin-A3 and plexin-B1. (a) Anti-phosphotyrosine western blotting of immunoprecipitated p220^{plex-A3} and p250^{plex-B1} proteins. plexin-B1 is larger since it contains an extra sequence between the second and the third MRS motif, in the extracellular domain (see Fig. 1). (b) The same immunoprecipitated samples underwent *in vitro* kinase assay in the presence of [γ^{32} P]ATP, Mg⁺⁺ and Mn⁺⁺ ions. The SDS-PAGE was treated with alkali in conditions known to eliminate the phosphate labeling of Ser/Thr residues and specifically preserving phosphotyrosines.

Figure 7

Plexin-A3 overexpression mediates cell repelling cues. (a) Epithelial kidney MDCK cells transfected to overexpress plexin-A3 (or mock transfected) were cocultured with mesenchymal KJ-29 or NIH-3T3 cells. After 16-30 hours, mixed cultures of control cells (upper panels) reached confluency and stopped growing: typically the epithelial cells formed islets (circled) surrounded by a fibroblasts lawn. In contrast, MDCKs overexpressing plexin-A3 (lower panels) overwhelmed the adjacent mesenchymal cells. The latter withdrew and selectively detached from the culture dish (dying cell clusters are indicated by arrowheads), and eventually epithelial cells only survived. To allow an easier detection of the mesenchymal cells, these were labeled with DiI before being plated in mixed cultures. (b) Plexin-A3 expressing cells do not induce apoptotic signal on repelled fibroblasts. Mixed cultures of NIH 3T3 and control or plexin-A3 overexpressing MDCKs were tested for the presence of TUNEL-AP positive cells. Apoptotic cells were not present in clusters of repelled cells (indicated by

arrows). The right panel shows a positive control where apoptosis was induced on the same cells by UV treatment. (c) Plexin-A3 over-expressing cells form very transient contacts with fibroblasts. Time-lapse video-microscopy of control and plexin-A3 overexpressing MDCK cells grown in presence of fibroblasts. On top, snap-shot images from the movie, taken every 50 minutes (real time). In the upper row is shown the persistent contact of a fibroblast (marked by an arrow) with an islet of control MDCK cells (marked by a star). In the lower row another fibroblast, instead, forms a transient contact with an islet of plexin-A3 transfected cells, which also, in turn, reshapes. At the bottom, the diagrams show the relative frequency of persistent, transient or very transient contacts between fibroblasts and MDCK cells.

DETAILED DESCRIPTION OF THE INVENTION

The reference works, patents, patent applications, and scientific literature, including accession numbers to GenBank database sequences, that are referred to herein establish the knowledge of those with skill in the art and are hereby incorporated by reference in their entirety to the same extent as if each was specifically and individually indicated to be incorporated by reference. Any conflict between any reference cited herein and the specific teachings of this specification shall be resolved in favor of the later. Likewise, any conflict between an art-understood definition of a word or phrase and a definition of the word or phrase as specifically taught in this specification shall be resolved in favor of the latter.

Four novel human plexins have been identified: plexin-B2, plexin-B3, plexin-D1 and Plexin A-4. Plexin-A4 is located on human chromosome 7 and is a family member of the plexin-A subfamily which also includes plexin-A1 (alternatively named plexin-1/NOV), plexin-A2 (alternatively named plexin-2/OCT) and plexin-A3 (alternatively named plexin-2/SEX). Plexin-B2 and plexin-B3 are located on human chromosome 22 and chromosome X, respectively, and are family members of the plexin-B subfamily which also includes plexin-B1 (alternatively named SEP). Plexin-B3 maps very close to the plexin-A3 genomic locus on Xq28. Plexin-D1 is the first identified member of the plexin-D subfamily and is atypical of any of the other subfamilies. A fourth subfamily of plexins, the plexin-C subfamily, is defined by VESPR (now plexin-C1).

The four novel plexins as described herein have in their extracellular domains regions of homology with two other protein families: (a) Scatter Factors Receptors, encoded by the *MET* oncogene family (Tamagnone and Comoglio, 1997 *supra*), and (b)

Semaphorins (Kolodkin et al. (1993) *supra* (Figure 1b). In particular, plexins and Met-like receptors contain short cysteine-rich motifs, termed "Met Related Sequences" (MRS), whose minimal consensus is: C-X(5-6)-C-X(2)-C-X(6-8)-C-X(2)-C-X(3-5)-C (Maestrini et al., 1996 *supra*); Tamagnone and Comoglio, 1997 *supra*); blue boxes in Fig. 1B). The proteins of the Met family contain a single MRS (in their receptor β chains), whereas in plexin family members there are two/three repeated MRS motifs. Furthermore, all plexin family members contain in their extracellular moiety a 500 amino acid region similar to the sema domain of semaphorins (Kolodkin et al. (1993) *supra*; Winberg et al., 1998 *supra*); yellow boxes in Fig. 1B. The MRS motif is proposed to function as protein-protein interaction domain.

The cytoplasmic domain of plexins contains a ~600 amino acid domain which we term the SP domain ("Sex and Plexins", marked in green in Fig. 1B) that is highly conserved within the family (57-97% similarity) and in evolution (over 50% similarity between invertebrates and humans). The SP domain does not share homology with any known protein. It includes a number of potential tyrosine phosphorylation sites, but lacks the typical motifs of catalytic tyrosine kinases. Interestingly, the predicted secondary structure of the SP domain includes long conserved alpha helices, typically found in protein-protein interaction modules. Furthermore, there are several dihydrophobic amino acid motifs (such as LL or LI), known to mediate the internalization and downregulation of transmembrane receptors (Sandoval, I.V. and Bakke O. (1994). Targeting of membrane proteins to endosomes and lysosomes. Trends in Cell Biology 4, 292-297).

The present invention also demonstrates that plexins can form complexes with neuropilins, which in turn demonstrates that a receptor for semaphorins can be hetero-oligomers of plexins and neuropilins. As demonstrated by in situ mRNA expression analysis, plexins and neuropilins are in fact simultaneously expressed in several neuronal populations during embryonic development. The plexin-neuropilin complex predates ligand binding, since the association is not influenced by the presence of class 3 semaphorins. That the observed plexin-neuropilin complexes are formed in *cis* is furthermore supported by the experimental conditions used (cotransfection of isolated cells with the two constructs). An interaction in *trans* might also be envisioned (considering that plexins and semaphorins share similar *sema* domains), however by

analyzing mixed cultures of cells separately transfected with plexins and neuropilins we did not isolate associated complexes (data not shown).

We observed that the main semaphorin binding domain of neuropilins (CUB domain (Giger, R.J., Urquhart, E.R., Gillespie, S.K., Levengood, D.V., Ginty, D.D., and Kolodkin, A.L. (1998) "Neuropilin-2 is a receptor for semaphorin IV: insight into the structural basis of receptor function and specificity." *Neuron* 21, 1079-1092; Nakamura, F., Tanaka, M., Takahashi, T., Kalb, R.G., and Strittmatter, S.M. (1998) "Neuropilin-1 extracellular domains mediate semaphorin D/III-induced growth cone collapse" [In Process Citation]. *Neuron* 21, 1093-1100; Chen et al. 1998 *supra*) is not required for the interaction with plexins, as indicated by the association of the relevant Neuropilin-2 deletion construct with plexin-B1 (not shown). A ternary complex, where neuropilins use two distinct protein modules to form a bridge between the sema domain of semaphorins and the sema domain of plexins is thus contemplated. It is further contemplated that plexins are the functional partners of neuropilins, required for transducing signals mediated by semaphorins, preferably class 3 semaphorins. For example, in flies, which lack both neuropilins and class 3 semaphorins, D Plex A appears sufficient as a functional receptor for Sema 1a, a transmembrane class 1 semaphorin (Winberg et al., 1998 *supra*). Further support that plexins are functional coreceptors for secreted semaphorins is demonstrated in an experiment that shows that a truncated plexin-A1 construct expressed in *Xenopus* spinal neurons abolishes repulsive responses to Sema3A without markedly affecting attractive responses to netrin-1. These results are consistent with the involvement of plexins.

The intracellular signals transduced by plexins are still largely obscure. The cytoplasmic domain of plexins is large and highly conserved within and across species and contains stretches of alpha helices, which are putative protein-protein interaction domains, and could thus mediate the association with cytosolic partners. We demonstrate herein that the cytoplasmic domain of plexins can be tyrosine phosphorylated, suggesting that, like other receptors devoid of intrinsic catalytic activity, plexins may signal by associating a tyrosine kinase (Stahl, N. and Yancopoulos, G.D. (1993). The alphas, betas, and kinases of cytokine receptor complexes. *Cell* 74, 587-590; Glass, D.J., Bowen, D.C., Stitt, T.N., Radziejewski, C., Bruno, J., Ryan, T.E., Gies, D.R., Shah, S., Mattsson, K., Burden, S.J., DiStefano, P.S.,

Valenzuela, D.M., DeChiara, T.M., and Yancopoulos, G.D. (1996). Agrin acts via a MuSK receptor complex. *Cell* 85, 513-523).

In addition, we show herein that expression of plexins, particularly plexin-A3, mediates cell-repelling cues. By time-lapse video-microscopy we observed a true repelling effect on fibroblasts. Intriguingly, we observed that -upon interaction with fibroblasts- also the islets of plexin-A3 MDCKs at times reshaped. This may be explained by the existence of intra-epithelial repelling cues, balanced by the attractive forces exerted by epithelial cell junctions.

Moreover we have demonstrated that in the nervous system (i.e. *Drosophila*), that defasciculating motor axons co-express both Plexin A and one of its interacting partners, the transmembrane semaphorin Sema-1a (Winberg et al., 1998 *supra*). This demonstrates that plexins act *in vivo* either as receptors or ligands for cell surface semaphorins, which in turn can transduce intracellular signals, as reported for ephrins (Holland et al., 1996 *supra*). Semaphorins, therefore, besides being pivotal in axon guidance, have a general role in morphogenesis and tissue remodeling by mediating cell-repelling cues via their interactions with plexins.

Accordingly, in a first aspect, the invention provides an isolated nucleic acid molecule encoding a novel human plexin polypeptide. By "plexin polypeptide" is meant a member of the plexin family comprising an amino acid sequence that shares at least 60% amino acid sequence homology with SEQ ID NOS: 2 (plexin B-2), 4 (plexin B-3), 6 (plexin D-1) or 8 (plexin A-4), preferably, at least 65% sequence homology, more preferably, at least 70% sequence homology, more preferably, at least at least 75% sequence homology, more preferably, at least 80% sequence homology, still more preferably at least 85% sequence homology, even more preferably, at least 90% sequence homology, and most preferably at least 95% sequence homology with SEQ ID NOS: 2, 4, 6 or 8. Plexin polypeptides of the invention are useful for modulating cell growth (i.e. nerve) and immune regulation.

As used herein, by "modulating" is meant increasing or decreasing cell growth. By "cell growth" is meant any change in cell number or size, including, without limitation, increase or decrease in cell number, increase or decrease in rate of cell division, increase or decrease in rate of cell death, and/or increase or decrease in cell size. Standard methods for measuring cell growth include standard apoptosis assays (e.g., TUNEL assays, DNA fragmentation, trypan blue exclusion) and cell proliferation assays

(*e.g.*, ³H-thymidine incorporation). It will be appreciated that the degree of modulation of cell growth provided by a plexin polypeptide in a given assay will vary, but one of skill in the art can readily determine the statistically significant change in cell growth of a cell exposed to a plexin polypeptide.

5 By "immune regulation" is meant increasing or decreasing the biological functions of immune cells (*i.e.*, cells involved in an immune response). Immune cells include, without limitation, lymphocytes (T and B), NK cells, dendritic cells, myeloid cells (*e.g.*, macrophages and neutrophils), and other hematopoietic cells involved in an immune response.

10 By "nucleic acid molecule" or "nucleic acid" as used herein, is meant any deoxyribonucleic acid (DNA) or ribonucleic acid (RNA), including, without limitation, complementary DNA (cDNA), genomic DNA, RNA, heteronuclear RNA (hnRNA), messenger RNA (mRNA), DNA/RNA hybrids, or synthetic nucleic acids (*e.g.*, an oligonucleotide) comprising ribonucleic and/or deoxyribonucleic acids or synthetic
15 variants thereof. The nucleic acid of the invention includes, without limitation, an oligonucleotide or a polynucleotide. The nucleic acid can be single stranded, or partially or completely double stranded (duplex). Duplex nucleic acids can be homoduplex or heteroduplex.

By "polypeptide" is meant any molecule comprising two or more amino acids
20 joined together with a peptide bond, regardless of length or post-translational modifications (*e.g.*, without limitation, glycosylation, lipidation, acetylation, or phosphorylation). Useful plexin polypeptides of the invention include, without limitation, the full length plexin polypeptides having the amino acid sequence of SEQ ID NOS: 2, 4, 6, 8 or 10;; an extracellular domain of the polypeptide having the amino
25 acid sequence 1 to 1199 of SEQ ID NO: 2; 1 to 1099 of SEQ ID NO: 4; 1 to 1270 of SEQ ID NO: 6 or 1 to 199 of SEQ ID NO: 8, with its associated signal peptide; or an extracellular domain of the polypeptide having the amino acid sequence 19 to 1199 of SEQ ID NO: 2; 24 to 1099 of SEQ ID NO: 4; or 43 to 1270 of SEQ ID NO: 6, lacking its associated signal peptide; an intracellular domain of the polypeptide having the
30 amino acid sequence of SEQ ID NOS: 2, 4, 6 or 8; and polypeptides, the amino acid sequence of which comprises about residues 1-18 (putative signal sequence), 19-518 (sema domain), 451-530 (1° MRS), 601-680 (2° MRS), 751-830 (3° MRS), 800-1010 (G-P repeats) or 1196-1215 (putative transmembrane domain) of SEQ ID

NO: 2; about residues 1-23 (putative signal sequence), 24-507 518 (sema domain) or 1100-1119 (putative transmembrane domain) of SEQ ID NO: 4; or about residues 1-42 (putative signal sequence), 43-600 (sema domain), 541-620 (1° MRS), 691-770 (2° MRS), 831-910 (3° MRS), 900-1110 (G-P repeats) or 1270-1293 (putative transmembrane domain) of SEQ ID NO: 6; or about residue 8-49 (1° MRS) or 154-199 (2° MRS) of SEQ ID NO: 8.

By "isolated" is meant a compound (*e.g.*, a nucleic acid molecule or a protein) that has been separated from components (*e.g.*, nucleic acid molecules, proteins, lipids, and/or carbohydrates) which naturally accompany it. Water, buffers, and other small molecules (*e.g.*, molecules having a molecular weight of less than about 1000 daltons) may accompany an isolated compound of the invention. Preferably, an isolated compound is at least 70%, by weight, free from components which naturally accompany it. More preferably, an isolated is at least 75%, by weight, free from components which naturally accompany it; still more preferably, at least 80%, by weight, free; even more preferably, at least 85%, by weight, free; and even more preferably, at least 90%, by weight, free from components which naturally accompany it. Most preferably, a substantially purified compound is at least 95%, by weight, free from components which naturally accompany it.

Where the isolated compound is a nucleic acid molecule, the isolated nucleic acid molecule is separated from other nucleic acids (*e.g.*, genes or transcripts) or proteins which, in the naturally-occurring genome of the organism from which the nucleic acid molecule was derived, flanked the nucleic acid molecule. Isolated nucleic acid molecules therefore include, without limitation, a recombinant nucleic acid molecule incorporated into a plasmid or other vector (*e.g.*, a replication-defective virus); a recombinant nucleic acid molecule incorporated into the genome of a prokaryotic or eukaryotic organism; or a nucleic acid molecule which exists as a separate molecule independent of other nucleic acids (*e.g.*, a PCR product, a chemically synthesized nucleic acid molecule, or a nucleic acid molecule produced by restriction endonuclease digestion). Purification of a nucleic acid molecule can be accomplished and measured by any standard method including, without limitation, sequence analysis, chemical synthesis, PCR, CsCl gradient, phenol:chloroform extraction, ethanol precipitation, Southern or Northern blotting analysis followed by band extraction and purification, and

high performance liquid chromatography (HPLC; see, *e.g.*, Fisher (1980) Laboratory Techniques in Biochemistry and Molecular Biology, Work and Burdon (eds.), Elsevier).

Thus, in one non-limiting example, to obtain an isolated nucleic acid molecule encoding a plexin polypeptide, a nucleic acid molecule is chemically synthesized on a standard oligonucleotide synthesis machine. The resulting single stranded molecule is then subjected to second strand synthesis to form a duplex DNA molecule, which is then ligated into a plasmid capable of replication in a prokaryotic or eukaryotic cell. The nucleic acid molecule is then replicated in the cell, purified (*e.g.*, by CsCl gradient), and subjected to sequence analysis.

In certain embodiments of the first aspect of the invention, the nucleic acid molecule has a nucleic acid sequence comprising SEQ ID NOS: 1, 3, 5, 7 or 9. Preferably, the nucleic acid molecule of the invention has not more than 500 nucleotides flanking each of the 5' and 3' ends of SEQ ID NOS: 1, 3, 5, 7 or 9. In certain embodiments, the plexin polypeptide has an amino acid sequence that comprises SEQ ID NOS: 2, 4, 6, 8 or 10. Preferably, the plexin polypeptide of the invention has not more than 50 amino acid residues flanking each of the N-terminal and C-terminal ends of SEQ ID NOS: 2, 4, 6, 8 or 10.

In certain embodiments of the first aspect of the invention, the nucleic acid molecule hybridizes under stringent conditions (as defined herein) to SEQ ID NOS: 1, 3, 5, 7 or 9.

The invention also includes nucleic acid molecules that hybridize under stringent hybridization conditions (as defined herein) to all or a portion of the nucleotide sequence represented by SEQ ID NOS: 1, 3, 5, 7 or 9 or its complement. The hybridizing portion of the hybridizing nucleic acid is at least 80%, *e.g.*, at least 95%, or at least 98%, homologous to the sequence of a portion or all of a nucleic acid encoding a polypeptide having the amino acid sequence of SEQ ID NOS: 2, 4, 6, 8 or 10, or its complement. Hybridizing nucleic acids of the type described herein can be used, for example, as a cloning probe, a primer (*e.g.*, a PCR primer) or a diagnostic probe.

Hybridization of the oligonucleotide probe to a nucleic acid sample typically is performed under stringent conditions. Nucleic acid duplex or hybrid stability is expressed as the melting temperature or T_m , which is the temperature at which a probe dissociates from a target DNA. This melting temperature is used to define the required stringency conditions. If sequences are to be identified that are related and substantially

identical, rather than identical, then it is useful to first establish the lowest temperature at which only homologous hybridization occurs with a particular concentration of salt (e.g., SSC or SSPE). Then, assuming that 1% mismatch results in a 1°C decrease in the T_m , the temperature of the final wash in the hybridization reaction is reduced

5 accordingly (for example, if the sequences have > 95% identity with the probe are sought, the final wash temperature is decreased 5°C). In practice, the change in the T_m can be between 0.5 C and 1.5 C per 1% mismatch. "Stringent conditions" involve hybridization at 68°C in 5x SSC/5x Denhardt's solution/1.0% SDS, and washing in 0.2xSSC/0.1% SDS at room temperature. "Moderately stringent conditions" include
10 washing in 3xSSC at 42°C. The parameters of salt concentration and temperature can be varied to achieve the optimal level of identity between the probe and the target nucleic acid. Additional guidance regarding such conditions is readily available in the art, for example, by Sambrook *et al.*, *supra*; and Ausubel *et al.*, *supra*.

Nucleic acid sequence homology (as well as amino acid sequence homology) can
15 be measured according to standard methods. Unless otherwise specified, as used herein used herein, "percent homology" of two amino acid sequences or of two nucleic acids is determined using the algorithm of Karlin and Altshul (*Proc. Natl. Acad. Sci. USA* 87: 2264-2268, 1990), modified as in Karlin and Altschul (*Proc. Natl. Acad. Sci. USA* 90: 5873-5877, 1993). Such an algorithm is incorporated into the NBLAST and XBLAST
20 programs of Altschul et al. (*J. Mol. Biol.* 215: 403-410, 1990). BLAST nucleotide searches are performed with the NBLAST program, e (score) = 100, word length = 12, to obtain nucleotide sequences homologous to a nucleic acid molecule of the invention. BLAST protein searches are performed with the XBLAST program, e (score) = 50, word length = 3, to obtain amino acid sequences homologous to a reference polypeptide (e.g.,
25 SEQ ID NO: 2). To obtain gapped alignments for comparison purposes, Gapped BLAST is utilized as described in Altschul et al. (*Nucleic Acids Res.* 25: 3389-3402, 1997).

When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (e.g., XBLAST and NBLAST) are used, namely $e=10$; $w=11$ for nucleic acid; $w=3$ for amino acid (the Blosum 62 scoring matrix); low complexity
30 sequence filtering. The default settings of BLAST emphasize regions of local alignment to detect relationships among sequences which share only isolated regions of similarity (Altschul et al., *J. Mol. Biol.* 215: 403-410 (1990)). See <http://www.ncbi.nlm.nih.gov>.

Thus, in a non-limiting example to obtain an isolated nucleic acid molecule encoding a plexin polypeptide, a nucleic acid molecule having the sequence of SEQ ID NOS: 1, 3, 5 or 7 is used to probe a cDNA library under stringent conditions according to standard techniques (see., *e.g.*, Ausubel *et al.*, *supra*). Upon identification of a positive
5 clone (*i.e.*, a clone that hybridizes to SEQ ID NOS: 1, 3, 5 or 7 under stringent conditions), that clone is expanded and subjected to sequence analysis. A nucleic acid molecule having a nucleic acid sequence that is at least 70% identical, preferably at least 75% identical, more preferably, at least 80% identical, still more preferably at least 85% identical, even more preferably, at least 90% identical, and most preferably at least 95%
10 identical (as measured by the basic BLAST-program of NCBI on default settings) to SEQ ID NOS: 1, 3, 5 or 7 is a nucleic acid molecule of the invention.

In a second aspect, the invention provides four novel isolated plexin polypeptides.

"Isolated" is as defined for the first aspect of the invention. Where the isolated compound is a polypeptide, the isolated polypeptide is separated from organic molecules,
15 such as nucleic acid molecules, polypeptides, and/or carbohydrates, which, in the naturally-occurring organism from which the polypeptide was derived, accompany the polypeptide. Isolated polypeptides therefore also include a recombinant polypeptide (*e.g.*, a human polypeptide expressed in an insect cell), or a chemically synthesized polypeptide. Purification of a polypeptide can be accomplished and measured by any
20 standard method including, without limitation, chemical synthesis, recombinant polypeptide expression in prokaryotic or eukaryotic cells, affinity chromatography, Western blotting analysis, SDS-PAGE analysis, and/or HPLC.

In accordance with this aspect, the invention provides all derivatives, mutants, truncations, and/or splice variants of the four novel plexin polypeptides, so long as these
25 derivatives, mutants, truncations, and/or splice variants share at least 60% amino acid sequence homology with SEQ ID NOS: 2, 4, 6 or 8, preferably, at least 65% sequence homology, more preferably, at least 70% sequence homology, more preferably, at least at least 75% sequence homology, more preferably, at least 80% sequence homology, still more preferably at least 85% sequence homology, even more preferably, at least 90%
30 sequence homology, and most preferably at least 95% sequence homology with SEQ ID NOS: 2, 4, 6 or 8 as determined using the basic BLAST program of the National Center for Biotechnology (NCBI; National Library of Medicine, Bethesda, MD), using the

default settings defined therein using the sequence of the four novel plexin derivative, mutant, truncation and/or splice variance as the probe.

Preferred plexin polypeptide derivatives include polypeptides whose sequences differ from the sequence given in SEQ ID NOS: 2, 4, 6 or 8, by one or more conservative amino acid substitutions, or by one or more non-conservative amino acid substitutions, deletions or insertions which do not abolish the biological activity of the plexins. Conservative amino acid substitutions typically include the substitution of one amino acid for another with similar biochemical characteristics, such as polarity, size, and/or charge. Non-limiting examples of conservative substitutions are substitutions within the following groups: valine, glycine, glycine, alanine, valine, isoleucine, leucine; aspartic acid, glutamic acid, asparagine, glutamine; serine, threonine; lysine, arginine, phenylalanine, and tyrosine.

Useful methods for mutagenesis to generate plexin mutants are known in the art (see, *e.g.*, Sambrook *et al.*, *supra*; Ausubel *et al.*, *supra*). Preferred methods for mutagenesis are described in PCT Publication WO99/12965 and include PCR mutagenesis and saturation mutagenesis. A library of random amino acid sequence variants can also be generated by the synthesis of a set of degenerate oligonucleotide sequences.

In certain embodiments of the second aspect of the invention, the plexin polypeptide has a sequence comprising the sequence of SEQ ID NOS: 2, 4, 6 or 8. In one non-limiting example, in accordance with the invention, an isolated plexin polypeptide comprising the sequence of SEQ ID NOS: 2, 4, 6 or 8 can chemically synthesized according to standard techniques (*e.g.*, at a commercial peptide generating facility).

For example, a putative plexin polypeptide is purified and subjected to N-terminal sequencing to determine its amino acid sequence. The amino acid sequence of the polypeptide is then compared to SEQ ID NOS: 2, 4, 6, 8 or 10 (as measured by the basic BLAST program of NCBI on default settings). A polypeptide that shares at least 60% homology with SEQ ID NOS: 2, 4, 6, 8 or 10 is a plexin polypeptide of the invention.

In another example, purification of a plexin polypeptide is facilitated by the addition of a tag to the polypeptide that enables purification of the tagged polypeptide.

Non-limiting examples of a tag include a hemagglutinin (HA) tag, a his tag, a GST tag, a

FLAG-tag, and a myc tag. Thus, a nucleic acid molecule of the first aspect is engineered using standard molecular biology techniques to incorporate the nucleic acid sequence encoding the tag. The engineered nucleic acid molecule is then introduced and positioned for expression in an appropriate cell to produce the recombinant tagged polypeptide, which can then be readily purified by binding of the tag to its substrate. For example, the his tag binds to Ni-NTA agarose. Likewise, a GST (glutathione S-transferase) tag binds to glutathione agarose beads. Both his tag and GST tag expression and purification kits are commercially available from PharMingen (San Diego, CA). Likewise, myc-tagged plexin polypeptide are produced by cells introduced with a nucleic acid molecule encoding the tagged protein and positioned for expression in the cell.

It will be appreciated that particularly useful polypeptides of this aspect of the invention are secreted by the cell in which they are produced, thus facilitating purification of the polypeptide from the culture media in which the cells have been maintained, without requiring lysis of the cell.

In a third aspect, the invention provides a cell engineered to comprise a nucleic acid molecule encoding one of the four plexin polypeptides. By "engineered" is meant that the cell of the invention has been modified by standard molecular biology techniques. Where the cell is "engineered to comprise a nucleic acid molecule," standard molecular biology techniques have been employed to introduce the indicated nucleic acid molecule into the cell, either by transformation or transfection of the cell with a plasmid, or by infection or transduction of the cell with a recombinant virus.

The nucleic acid molecule of the first aspect of the invention is preferably subcloned into a plasmid or vector (for example, but not limited to, a vector used to generate a recombinant virus), wherein the nucleic acid molecule is positioned for expression in the plasmid or vector. The plasmid or vector is then introduced into a cell by standard techniques to produce an engineered cell in accordance with the third aspect of the invention.

In certain embodiments of the third aspect, the cell is a prokaryotic cell (*e.g.*, a bacterium). For example, *E. coli* cells (*e.g.*, DH5 α) are transformed (using, *e.g.*, electroporation) with a bacterial plasmid (*i.e.*, a plasmid containing an *E. coli* origin of replication) containing a nucleic acid molecule of the first aspect of the invention. The transformed bacteria are selected using, for example, an antibiotic-resistance encoding nucleic acid molecule (*e.g.*, ampicillin resistance) on the plasmid such that the antibiotic

resistance protein is expressed by the transformed bacteria. The transformed bacteria are then propagated, and can be cryopreserved and stored frozen in glycerol.

Those of skill in the art will appreciate that in accordance with the third aspect of the invention, a nucleic acid molecule encoding one of the four plexin polypeptides may be introduced into a large variety of cells. For example, a nucleic acid molecule
5 encoding one of the four plexin polypeptides can be introduced into prokaryotic cells (e.g., bacteria), and any eukaryotic cell into which an exogenous nucleic acid molecule may be introduced. Thus, in certain embodiments of the third aspect of the invention, the cell is a eukaryotic cell. Eukaryotic cells according to this aspect of the invention that
10 comprise a nucleic acid molecule encoding one of the four plexin polypeptides include, without limitation, yeast cells, plant cells, insect cells, and mammalian cells. Within the category of mammalian cells are cells from any mammalian species (including, without limitation, mouse, hamster, monkey, human), of any lineage (including, without limitation, lymphocyte, fibroblast, stem cell), and may be an immortalized cell, or a non-
15 immortalized cell. Cells, as well as plasmids and/or vectors (e.g., vectors that can be packaged to form infectious virus particles), are commercially available, for example, from the American Type Culture Collection ("ATCC"; Manassas, VA).

In certain embodiments of the third aspect of the invention, the nucleic acid molecule is positioned for expression in the cell. By "positioned for expression" is
20 meant that the nucleic acid molecule is operably linked to at least one regulatory sequence which directs the transcription and translation of the nucleic acid molecule in a cell, such that the cell engineered to comprise the nucleic acid molecule produces (i.e., expresses) the protein encoded by the nucleic acid molecule. By "operably linked" is meant that the nucleic acid molecule and the regulatory sequence are connected in a such
25 a way as to permit expression of the nucleic acid molecule when the nucleic acid molecule is present in a cell. Regulatory sequences include, without limitation, promoters, enhancers, IRES sequences, and polyadenylation signals. Since plexin polypeptides are involved in immune regulation and the modulation of cell growth, it may be desirable to operably link a nucleic acid molecule encoding one of the four plexin
30 polypeptides to an inducible promoter.

The four plexin polypeptides that are encoded by the nucleic acid molecules do not necessarily include the transmembrane domain of the four plexin polypeptides, and so may be produced by the cell as an intracellular polypeptide or a soluble secreted

polypeptide. For example, if the polypeptide fragment is secreted by the cell, it can be purified from the conditioned growth media of the transfected cells, without having to lyse the cells. Likewise, although a soluble intracellular polypeptide fragment is purified from only lysed cells, the fragment, being soluble, does not have to be extracted from the cell membrane; thus, different lysis conditions may be used to obtain purified soluble intracellular polypeptide fragment as compared to the lysis conditions required to obtain purified full length plexin polypeptides (which has a transmembrane domain).

Protein expression systems have been established for a variety of cells and are known to those of skill in the art. Cells are also commercially available from the ATCC, and a variety of protein expression system kits are commercially available from, for example, Invitrogen Corp. (Carlsbad, CA), Clontech Laboratories (Palo Alto, CA), PharMingen (San Diego, CA), Promega Corp. (Madison, WI), and Stratagene (La Jolla, CA).

For example, a nucleic acid molecule encoding one of the four plexin polypeptides is operably linked to bacterial regulatory sequences (*e.g.*, T7 late promoter or bacteriophage regulatory sequences), and the resulting nucleic acid molecule is used to transform bacterial cells, where the transformed bacterial cells produce one of the four plexin polypeptides. In another example, a nucleic acid molecule encoding one of the four plexin polypeptides is operably linked to baculovirus regulatory sequences in a baculovirus vector. Recombinant baculovirus are then generated and used to transduce insect cells (using, for example, the expression kit commercially available from Clontech Laboratories). The transduced insect cells comprise a nucleic acid molecule encoding one of the four plexin polypeptides positioned for expression in the insect cell, and thus produce one of the four plexin polypeptides.

Mammalian cells are widely used as protein expression systems. For example, a mammalian cell may be transduced with a recombinant retrovirus or adenovirus comprising a nucleic acid molecule encoding one of the four plexin polypeptides operably linked to regulatory sequences that are either endogenous to the particular virus or exogenous to the virus (*e.g.*, a CMV promoter in a retroviral vector). The transduced mammalian cell is then propagated *in vitro* in tissue culture, *in vivo* (*e.g.*, in an immunocompromised animal), and/or cryopreserved and stored frozen in DMSO.

In another example, mammalian cells are transfected with an expression plasmid comprising a nucleic acid molecule encoding one of the four plexin polypeptides

operably linked to one or more regulatory sequences on the plasmid. By "expression plasmid" is meant a plasmid in which an inserted nucleic acid molecule of interest (*e.g.*, encoding one of the four plexin polypeptides, a plexin chimeric molecule, or tagged plexin polypeptide) is operably linked to at least one regulatory sequence such that when
5 the expression plasmid containing the inserted nucleic acid molecule of interest is introduced (*e.g.*, by transfection) into a cell, the inserted nucleic acid molecule is positioned for expression in that cell. The nucleic acid molecule in the expression plasmid, upon being introduced into the cell, is thus positioned for expression in that cell, and enables the cell to produce one of the four plexin polypeptides encoded by the
10 nucleic acid molecule.

In one non-limiting example, a nucleic acid molecule according to the first aspect of the invention is inserted into a standard mammalian expression plasmid (*e.g.*, pCDNA3.1 commercially available from Invitrogen Corp., Carlsbad, California), such that the inserted nucleic acid molecule encoding one of the four plexin polypeptides is
15 operably linked to the regulatory sequences in the mammalian expression plasmid. Mammalian cells are then transfected with this expression plasmid (using, *e.g.*, CaPO_4 or DEAE-dextran). Where the expression plasmid contains an antibiotic-resistance encoding nucleic acid molecule (*e.g.*, neomycin resistance on the pCDNA3.1 plasmid) such that the antibiotic resistance protein is expressed by the transfected cells, transfected
20 cells may be selected for the ability to grow in the presence of the antibiotic. The transfected cells may then be propagated and cryopreserved and stored in frozen in DMSO.

In a fourth aspect, the invention provides an isolated nucleic acid molecule encoding a chimeric molecule comprising at least two segments, wherein one of the
25 segments comprises one of the four plexin polypeptides. By "chimeric molecule" is meant a protein that comprises at least two segments of polypeptide joined together by any means, including, without limitation, a covalent bond (*e.g.*, peptide bond), a non-covalent bond (*e.g.*, ionic bond or hydrogen bond) or by a chemical crosslinker. It should be noted that one of the four plexin polypeptides that has been tagged is within the
30 definition of a chimeric molecule.

In certain embodiments of the fourth aspect of the invention, the nucleic acid molecule encoding the segment of a chimeric molecule comprising one of the four plexin

polypeptides hybridizes under stringent conditions to SEQ ID NO: 1, 3, 5 or 7.

"Stringent conditions" are as described above for the first aspect of the invention.

Standard molecular biology techniques may be employed to generate nucleic acid molecules encoding chimeric molecules according to the fourth aspect of the invention.

5 For example, a nucleic acid molecule encoding the extracellular domain of one of the four plexin polypeptides may be joined, in frame, to a nucleic acid molecule encoding the constant region of an immunoglobulin molecule (see, *e.g.*, Chamow S.M., Antibody Fusion Proteins, John Wiley & Sons, New York, 1999). By "in frame" is meant that a first nucleic acid molecule is ligated to a second nucleic acid molecule such that the each
10 of the amino acid sequences of the polypeptides encoded by each of the first and the second nucleic acid molecules is not frame-shifted.

In one non-limiting example, a chimeric molecule comprising the extracellular domain of one of the four plexin polypeptides including the amino acid sequence of SEQ ID NOS: 2, 4, 6 or 8 is generated. In this example, a nucleic acid molecule encodes
15 amino acid residue number 1(19) through about amino acid residue number 1199 of SEQ ID NO: 2; amino acid residue number 1(24) through about amino acid residue number 1099 of SEQ ID NO: 4; amino acid residue number 1(43) through about amino acid residue number 1270 of SEQ ID NO: 6 and amino acid residue number 1 through about amino acid residue number 199 of SEQ ID NO: 8 with its associated signal peptide
20 (parenthesis depicts about the beginning of the amino acid sequence of the extracellular domain lacking its signal peptide). This nucleic acid molecule is fused in frame with a nucleic acid molecule encoding the constant region of an immunoglobulin, such that the chimeric molecule encoded by the resulting nucleic acid molecule generally has the following structure:

25

N-terminus	extracellular domain of SEQ ID NO: 2 with or lacking its signal peptide	amino acids from the constant region of an Ig molecule	C-terminus
N-terminus	extracellular domain of SEQ ID NO: 4 with or lacking its signal peptide	amino acids from the constant region of an Ig molecule	C-terminus
N-terminus	extracellular domain of SEQ ID NO: 6 with or lacking its signal peptide	amino acids from the constant region of an Ig molecule	C-terminus
N-terminus	extracellular domain of SEQ ID NO: 8 with or lacking its signal	amino acids from the constant region of an Ig molecule	C-terminus

	peptide		
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The heavy chain class (*e.g.*, IgG, IgA, IgM, IgD, or IgE) can be varied in this chimeric molecule depending upon which constant region is used. Nucleic acid molecules encoding the constant region of various immunoglobulin (Ig) heavy chains are known
 5 (see, *e.g.*, Zettlmeissl et al., *DNA Cell Biol.* 9(5):347-53, 1990) Indeed, expression plasmids are available, into which the nucleic acid molecule of interest (*i.e.*, a nucleic acid molecule encoding an extracellular domain of the polypeptide of SEQ ID NO: 2; SEQ ID NO: 4; SEQ ID NO: 6; or SEQ ID NO: 8) can be inserted, and the resulting plasmid introduced into a cell to produce one of the four extracellular plexin-Ig chimeric
 10 molecule s (see, *e.g.*, Zettlmeissl et al., *supra*; Miller et al., *J. Exp. Med.* 178 (1): 211-222, 1993).

Any variety of chimeric molecule carrying the extracellular domains of one of the four plexin polypeptide may be generated. For example, the extracellular domain of one of the four plexin polypeptides can be myc-tagged, his-tagged, or FLAG tagged
 15 according to standard molecular biology techniques.

Such extracellular proteins are particularly useful for identifying ligands to which the extracellular domain of one of the four plexin polypeptides bind. For example, extracellular plexin-D1-Ig chimera can be immobilized on a protein A-sepharose column. Molecules suspected of binding the extracellular domain of plexin-D1 are added to the
 20 column, to which the molecule that binds to the extracellular domain of plexin-D1 adhere, and the non-binding molecules flow through the column. The extracellular plexin-D1-binding molecules are readily eluted, for example, by changing the pH or ion concentration of the elution buffer.

Extracellular plexin proteins are also used to identify cells expressing the ligand
 25 of plexin extracellular domain on their cell surface (and thereby also identify the ligand itself). For example, cells are incubated with a FLAG-tagged plexin extracellular domain chimeric molecule. A FLAG-tagged plexin extracellular domain chimeric molecule is generated. An anti-FLAG antibody that is detectably labeled is then added to the cells. By "detectably labeled" is meant any means for marking and identifying the presence of a
 30 molecule. Detectable labels include, without limitation, radioactive labels (*e.g.*, ³²P or ³⁵S) and fluorophore labels (*e.g.*, FITC, phycoerythrin, or rhodamine). For example, FITC-labeled anti-FLAG antibodies are commercially available from Babco, Richmond,

CA. The "stained" cells (*i.e.*, cells incubated first with the FLAG-tagged plexin extracellular domain chimeric molecule and then with the FITC-labeled anti-FLAG antibody), are then subjected to flow cytometry analysis to select those cells that are labeled with FITC, and so express a molecule that binds to the extracellular domain of one of the four plexin polypeptides. The FITC labeled cells are then further manipulated (*e.g.*, characterized to determine which cells express the plexin polypeptide ligand).

The ligand of the plexin extracellular domain is itself identified, for example, by lysing the cells, adding the lysate to one of the four plexin extracellular domain-Ig chimeric molecule columns described above, and purifying the ligand. The ligand is then sequenced by N-terminal sequencing.

In another non-limiting example, the intracellular domain of one of the four plexin polypeptides is used as "bait" in a yeast two-hybrid system to identify ligands that interact with the intracellular domain of one of the four plexins described herein. For general description of the two-hybrid system, see U.S. Patent Nos. 5,283,173; 5,468,614; and 5,695,941. In this example, a nucleic acid molecule encoding from about amino acid residue number 143 through at least amino acid residue number 214 of SEQ ID NO: 2 is inserted into a standard DNA binding domain expression plasmid (*e.g.*, the GAL4 DNA binding domain plasmid in the Interactor kit commercially available from PharMingen (San Diego, CA). (It will be understood that the nucleic molecule may encode amino acid residue number 138-148 through at least amino acid residue number 214 of SEQ ID NO: 2.) A variety of cDNA libraries in transcriptional activation domain vectors are available (*e.g.*, from Clontech, Palo Alto CA). The cDNA libraries are screened employing standard methods (see, *e.g.*, the methods employed in U.S. Patent No. 5,780,262) to identify cDNA clones encoding a ligand that binds to the intracellular domain of one of the four plexin polypeptides. One preferable cDNA library screened in this example is a cDNA library generated from an immune cell (*e.g.*, a lymphocyte or NK cell).

In a fifth aspect, the invention provides a purified chimeric molecule comprising one of the four plexin polypeptides. Methods for purifying proteins are as described for the second aspect of the invention.

In a sixth aspect, the invention provides a cell engineered to comprise a nucleic acid molecule encoding a chimeric molecule comprising at least two segments, wherein one of the segments comprises one of the four plexin polypeptides. As described for the

third aspect of the invention, a nucleic acid encoding a chimeric molecule comprising one of the four plexin polypeptides may be introduced into any variety of cells. In certain embodiments, the cell is a prokaryotic cell or a eukaryotic cell. In certain embodiments, the eukaryotic cell is a yeast cell or a mammalian cell (*e.g.*, a human cell).

5 In a seventh aspect, the invention provides an isolated binding agent that specifically binds one of the four plexin polypeptides, or specifically binds a chimeric molecule comprising a segment comprising one of the four plexin polypeptides. In certain embodiments, the plexin protein has an amino acid sequence comprising SEQ ID NOS:2, 4, 6 or 8.

10 By "specifically binds" is meant a binding agent (*e.g.*, an antibody) that binds to its specific target (*e.g.*, one of the four plexin polypeptides) with greater affinity than it binds to other molecules. Preferably, where the binding agent is an antibody, the antibody preferably specifically binds to its specific target with a dissociation constant (K_D) of at least 10^{-5} M, more preferably, 10^{-6} M, even more preferably 10^{-7} M, and most
15 preferably, the binding agent specifically binds to its specific target with a K_D of at least 10^{-8} M.

Preferably, the binding agent of this aspect of the invention is an antibody, such as a monoclonal antibody or a polyclonal antibody, or a fragment of an antibody that specifically binds one of the four plexin polypeptides. Standard methods may be
20 employed to generate both monoclonal and polyclonal antibodies that specifically bind to one of the four plexin polypeptides of the invention. See, *e.g.*, Ausubel et al., *supra*; Coligan, J.E. et al., Current Protocols in Immunology, John Wiley & Sons, New York (1991); and Delves, P.J., Antibody Production: Essential Techniques, John Wiley & Sons, New York (1997). Briefly, the plexin polypeptides of the present invention,
25 purified according to the methods described for the second aspect of the invention, are used to immunize rabbits (*e.g.*, for polyclonal antibodies) or mice (*e.g.*, for monoclonal antibodies) to generate antibody-mediated immunity to the four plexin polypeptides used to immunize the animal. For monoclonal antibodies, antibodies can be screened by, *e.g.*, ELISA, to identify those antibodies that show the highest affinity for the immunizing
30 plexin protein or polypeptide fragment. The cloned cell producing the high affinity monoclonal antibody can then be propagated *in vitro* (where the antibody is purified from the culture supernatant) or *in vivo* (where the antibody is purified from ascites fluid), and

can also be cryopreserved and stored frozen at, *e.g.*, -70°C in DMSO, to provide a potentially limitless supply of monoclonal antibody.

In addition to intact monoclonal and polyclonal antibodies, the invention also provides various antibody fragments, such as Fab, F(ab')₂, Fv, and sFv fragments.

5 Recombinant, chimeric, and humanized antibodies are also provided.

Recombinant "humanized antibodies" which specifically bind to one of the four plexin polypeptides can be synthesized according to methods known in the art (see, *e.g.*, Green L.L. *et al.*, *Nature Genetics* 7: 13-21, 1994 for fully humanized antibodies expressed in transgenic animals; see also U.S. Patent Nos: 5,693,761; 5,777,085; and 10 5,585,089). Humanized antibodies are chimeras comprising mostly human IgG sequences into which at least portions of the regions responsible for specific antigen-binding (*e.g.*, CDR's) have been inserted. Animals are immunized with the desired antigen, the corresponding antibodies are isolated, and the portion of the variable region sequences responsible for specific antigen binding are removed. The animal-derived 15 antigen binding regions are then cloned into the appropriate position of human antibody genes in which the antigen binding regions have been deleted. Humanized antibodies minimize the use of heterologous (*i.e.*, inter-species) sequences in human antibodies, and thus are less likely to elicit immune responses in the treated subject (see also, *e.g.*, U.S. Patent No. 5,807,715).

20 Construction of different classes of recombinant antibodies can also be accomplished by making chimeric or humanized antibodies comprising nonhuman variable domains and human constant domains (CH1, CH2, CH3) isolated from different classes of immunoglobulins. For example, antibodies with increased antigen binding site valencies can be recombinantly produced by cloning the antigen binding 25 site into vectors carrying the human chain constant regions (see, *e.g.*, Arulanandam *et al.*, *J. Exp. Med.* 177: 1439-1450, 1993).

In addition, standard recombinant DNA techniques can be used to alter the binding affinities of recombinant antibodies with their antigens by altering amino acid residues in the vicinity of the antigen binding sites. The antigen binding affinity of a 30 humanized antibody can be increased by mutagenesis based on molecular modeling (see, *e.g.*, Queen *et al.*, *Proc. Natl. Acad. Sci.* 86: 10029-10033, 1989).

Also provided in the invention are plexin polypeptide-specific single polypeptide chain antibodies (see general methods in U.S. Patent Nos. 4,946,788 and

4,704,692); single domain antibodies (Ward, E.S. et al., *Nature* 341: 544-546, 1989); and chimeric antibodies (U.S. Patent No. 4,816,567).

Binding agents that specifically bind the plexin polypeptides of the present invention are useful, for example, in determining expression levels of the plexin polypeptides in various tissues of the body, Western blotting analysis, and immunochromatography. Particularly, binding agents that specifically bind the plexin polypeptides are useful for binding the plexin polypeptide on a cell expressing the plexin polypeptide, thereby activating the cell.

A binding agent that specifically binds one of the four plexin polypeptides, for example, is effective as an immune modulator. Additional applications include, without limitation, an injectable formulation comprising a binding agent that specifically binds one of the four plexin polypeptides that is useful to antagonize activity in a disease involving aberrant immune regulation or a disease involving aberrant cell growth.

In an eighth aspect, the invention provides an isolated antisense oligonucleotide complementary to a portion of a nucleic acid molecule encoding one of the four plexin polypeptides. In certain embodiments, hybridization of the antisense oligonucleotide to the nucleic acid molecule inhibits transcription or translation of the nucleic acid molecule.

By two nucleic acid molecules being "complementary" to one another is meant that the first nucleic acid molecule (e.g., an oligonucleotide) is able to form Watson-Crick base pair hydrogen bonds (i.e., hybridize) with the second nucleic acid molecule to form a duplex. The first nucleic acid molecule is thus a "complement" of the second nucleic acid molecule.

The antisense oligonucleotides according to the invention are complementary to a region of a nucleic acid molecule (or a region at the intron/exon boundary of DNA or RNA) that encodes one of the four plexin polypeptides. Preparation of antisense oligonucleotides is well known (see, e.g., Agrawal et al., *Trends Biotechnol.* 10:152-158, 1992; U.S. Patent No. 5,149,798; Agrawal et al., *Proc. Natl. Acad. Sci. USA* 85:7079-7083, 1988; Froehler, *Tetrahedron Lett.* 27:5575-5578, 1986; and Bergot et al., *J. Chromatog.* 559:35-42, 1992).

In a ninth aspect, the invention provides a method for identifying a nucleic acid molecule encoding one of the four plexin polypeptides, comprising contacting a pool of candidate nucleic acid molecules with a nucleic acid molecule encoding one of the four

plexin polypeptides, wherein hybridization of the nucleic acid molecule encoding one of the four plexin polypeptides under stringent conditions to a candidate nucleic acid molecule identifies the candidate nucleic acid molecule as a nucleic acid molecule that encodes one of the four plexin polypeptides. According to this aspect of the invention, 5 "hybridization" and "stringent conditions" are as defined above for the first aspect of the invention. In certain embodiments, the nucleic acid molecule encoding one of the four plexin polypeptides has a nucleic acid sequence comprising SEQ ID NOS: 1, 3, 5 or 7.

It will be understood that the isolated plexin polypeptides according to the second aspect of the invention, the plexin chimeric molecules according to the fifth aspect of the invention, and binding agents that specifically bind the plexin polypeptides according to 10 the seventh aspect of the invention, are useful as therapeutics to treat an individual suffering from, or suspected of having, a disease or disorder involving aberrant immune regulation or an individual suffering from, or suspected of having, a disease or disorder involving aberrant cell growth, particularly nerve cell growth.

15 By "disease or disorder involving aberrant immune regulation" is meant any disease or disorder in which an abnormal immune response is generated in response to either self or foreign antigens. Thus, this definition includes, without limitation, autoimmune diseases (*e.g.*, lupus, inflammatory bowel disease, or Diabetes Type 1) and immunosuppressive diseases (*e.g.*, multiple sclerosis or rheumatoid arthritis).

20 By "disease or disorder involving aberrant cell growth" is meant any disease or disorder in which an abnormal amount of cell growth is observed. "Cell growth" is defined above. Thus, diseases and disorders involving aberrant cell growth include hyperplasia, neoplasia, and cancer, as well as degenerative diseases, such as neurodegenerative diseases.

25 Preferable therapeutically useful plexin polypeptides are soluble polypeptides (*e.g.*, lacking the hydrophobic transmembrane domain of the plexin polypeptides), particularly soluble polypeptide fragments that are secreted by the cell in which the fragment was produced. In a preferred embodiment the soluble plexin polypeptides are selected from the group consisting of plexin-A-1 (Maestrini et al. 1996 *supra*), plexin-A- 30 2 (Maestrini et al. 1996 *supra*), plexin-A-3 (Maestrini et al. 1996 *supra*), plexin-A-4, plexin-B-1 (Maestrini et al. 1996, *supra*), plexin-B-2, plexin-B-3, plexin-C1 (Comeau et al. 1998 *supra*), plexin-D-1...

In a tenth aspect, the invention provides a method for diagnosing a disease involving aberrant immune regulation or a disease involving aberrant cell growth, comprising comparing the amino acid sequence of one of the four plexin polypeptides from an individual suspected of having the disease with the amino acid sequence of one of the four plexin polypeptides from an unaffected individual, wherein the presence of a difference between the two amino acid sequences identifies the individual suspected of having the disease as having the disease. "Disease or disorder involving aberrant immune regulation" and "disease or disorder involving aberrant cell growth" are as defined above.

By "difference" in the amino acid sequence of one of the four plexin polypeptides from an individual suspected of having the disease or disorder as compared with the amino acid sequence of one of the four plexin polypeptides from an unaffected individual, is meant any mutation that changes the amino acid sequence including substitution, deletion, or addition of one or more amino acid residues.

Thus, in one nonlimiting example, one of the four plexin polypeptides is extracted from cells of an individual suspected of having a disease involving aberrant immune regulation (e.g., using an antibody according to the seventh aspect of the invention). The amino acid sequence of the plexin polypeptide is determined by N-terminal sequencing and compared to the amino acid sequence of one of the four plexin polypeptides from an unaffected individual (i.e., a normal individual of the same species that does not have a disease involving aberrant immune regulation or a disease involving aberrant cell growth). If there is a difference in the two amino acid sequences, the individual suspected of having a disease involving aberrant immune regulation is identified as having a disease involving aberrant immune regulation, and may be treated accordingly.

In certain embodiments of the tenth aspect, the amino acid sequence of the plexin polypeptide from the unaffected individual comprises the sequence of SEQ ID NO: 2, 4, 6, 8 or 10.

The following examples are intended to further illustrate certain preferred embodiments of the invention and are not limiting in nature. Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, numerous equivalents to the specific substances and procedures described herein. Such

equivalents are considered to be within the scope of this invention, and are covered by the following claims.

Practice of the present invention will employ, unless indicated otherwise, conventional techniques of cell biology, cell culture, molecular biology, microbiology, recombinant DNA, protein chemistry, and immunology, which are within the skill of the art. Such techniques are described in the literature. See, for example, **Molecular Cloning: A Laboratory Manual**, 2nd edition. (Sambrook, Fritsch and Maniatis, eds.), Cold Spring Harbor Laboratory Press, 1989; **DNA Cloning**, Volumes I and II (D.N. Glover, ed), 1985; **Oligonucleotide Synthesis**, (M.J. Gait, ed.), 1984; U.S. Patent No. 4,683,195 (Mullis et al.); **Nucleic Acid Hybridization** (B.D. Hames and S.J. Higgins, eds.), 1984; **Transcription and Translation** (B.D. Hames and S.J. Higgins, eds.), 1984; **Culture of Animal Cells** (R.I. Freshney, ed). Alan R. Liss, Inc., 1987; **Immobilized Cells and Enzymes**, IRL Press, 1986; **A Practical Guide to Molecular Cloning** (B. Perbal), 1984; **Methods in Enzymology**, Volumes 154 and 155 (Wu et al., eds), Academic Press, New York; **Gene Transfer Vectors for Mammalian Cells** (J.H. Miller and M.P. Calos, eds.), 1987, Cold Spring Harbor Laboratory; **Immunochemical Methods in Cell and Molecular Biology** (Mayer and Walker, eds.), Academic Press, London, 1987; **Handbook of Experiment Immunology**, Volumes I-IV (D.M. Weir and C.C. Blackwell, eds.), 1986; **Manipulating the Mouse Embryo**, Cold Spring Harbor Laboratory Press, 1986.

The following Examples are provided to illustrate the present invention, and should not be construed as limiting thereof.

EXAMPLES

Example 1

Identification and cDNA cloning of *plexins* and sequence analysis

Since the coding sequences of human *plexin-B1(SEP)*, *plexin-A2(OCT)* and
5 *plexin-A1(NOV)* were incomplete, we obtained the missing cDNA by RT-PCR; primers
were designed by homology to orthologous murine sequences and corresponding ESTs.
Updated database entries are X87904, X87831 and X87832, respectively. Partial cDNA
of *plexin-A4* was obtained by assembling five overlapping human ESTs (HGI THC
Report: THC203425), deriving from chromosome 7 specific cDNA pools. Another EST
10 from chr. 7 (clone 7B19F10) encodes the cytoplasmic domain of a plexin and
presumably derives from the same gene as *plexin-A4*. *Plexin-B2* cDNA was amplified
by RT-PCR starting from the partial cDNA sequences of clones *MM1* (Shinoura, N.,
Shamraj, O.I., Hugenholtz, H., Zhu, J.G., McBlack, P., Warnick, R., Tew, J.J., Wani,
M.A., and Menon, A.G. (1995). Identification and partial sequence of a cDNA that is
15 differentially expressed in human brain tumors. *Cancer Lett* 89, 215-221) and
KIAA0315 (Genbank database); the genomic locus of *SEP-B* was identified due to its
100% sequence identity with clone C22_311 from human chromosome 22. *Plexin-B3*
coding sequence was identified in the genomic sequence of ALD locus on human
chromosome Xq28, using the algorithms HEXON and GENIE. *Plexin-D1* was similarly
20 found in the genomic sequence of chromosome 3 (pac pDJ70i11). The genomic
sequence of *plexin-B1(SEP)*, in the region of the alternative splicing of the extracellular
domain, was obtained using the following primers: sense
5'GCAGCACCTGTGCACCCACAAGGC3' and antisense:
5'TGCAGGCTGGACGGGAGGATGAGG3'. The common donor site is
25 CCATCAG/gtgattgt (position 2028 from ATG); the alternative splice acceptor sites are:
(i) ccccttcag/AGCCC, leading to the canonical *plexin-B1* sequence, and (ii)
ctctctcag/GTGAT, leading to "plexin-B1 truncated" variant. All these new sequences
were analyzed using the algorithms BLAST2, NETPHOS (phosphorylation prediction
sites, by Nicolaj Blom), PH-PREDICT and Consensus Protein Secondary Structure
30 prediction at IBCP. The phylogenetic tree was generated using AllAll algorithm of the
Darwin sequence analysis system (at CBRG).

Example 2

Plexin cDNA expression constructs and protein analysis

Cell transfections were carried out by Calcium phosphate and DEAE-dextran methods, using 5-10 µg of each cDNA (1-2 µg each in case of cotransfections). For transient transfections in COS and BOSC-23 cells the cDNA was cloned in pCDNA3 or derived expression plasmids (Invitrogen). MDCK stable transfectants for *plexin-A3* were obtained using pCEP4 expression plasmid (Invitrogen); the selection was done in the presence of Hygromycin-B (100-200 µg/ml). *Plexin-A3* positive clones of MDCK cells were isolated from two independent transfections, and showed identical biological properties. *Plexin* and neuropilin expression constructs included a VSV- and myc-tag at the N' and C' protein termini, respectively, detected by monoclonal antibodies anti-VSV-G (cat. V-5507, Sigma) and anti-cMyc-tag (cat. OP10-100UG, Calbiochem). "Plexin-B1 truncated" splice variant was expressed from a cDNA fragment isolated by RT-PCR and VSV-tagged at the N' terminus: the encoded amino acid sequence spans up to aa 676 (including the *sema* domain and two MRS motifs). "Plexin-B1-*sema*" derives from a further deletion of the *plexin-B1* extracellular domain, and exclusively includes the *sema* domain. "Plexin-B1-Δ*sema*" protein mutant includes only the C' terminal half of *plexin-B1* extracellular domain, starting from amino acid 606, i.e. excluding *sema* domain and first MRS but including second and third MRS, transmembrane and intracellular domains.

For immunoprecipitations, cells were lysed with EB buffer (20 mM Tris-HCl pH 7.4, 5 mM EDTA, 150 mM NaCl, 10% glycerol, 1% Triton X-100), in the presence of a cocktail of protease inhibitors and 1mM Na-orthovanadate. Immunoprecipitations were performed at 4°C for 4h with the appropriate antibodies; high stringency washes were performed, in the presence of 1 M LiCl.

For *in vitro* kinase assays, immunopurified proteins were incubated with kinase buffer (50 mM Hepes, 100 µM DTT, 5 mM MnCl₂, 5 mM MgCl₂) in the presence of redivue 5 µCi [γ-³²P] ATP (Amersham) for 10 minutes at 4°C in agitation. Samples were then submitted to SDS-PAGE and autoradiography, or analysed using a Phosphor-Imager system (Molecular Dynamics). Alkali treatment of the polyacrilamide gels was performed with 1M KOH for two hours at 55°C.

Western blots were performed according to standard methods. Specific detection of phospho-tyrosines was done with PY20 MoAb (Trasduction laboratories). Final detection was done with ECL system (Amersham).

Example 3

Semaphorin-SEAP binding assays

Soluble forms of Semaphorin extracellular domains were expressed as chimeric molecules with placental Secreted Alkaline Phosphatase (SEAP) and harvested from the conditioned media of transiently transfected COS or BOSC-23 cells. Serum-free media were concentrated over 100 times using Centricon Plus-20 filters (Millipore) with a molecular weight cutoff of 100 kDa. The AP activity of these media was assessed as described (Flanagan, J.G. and Leder, P. (1990). The kit ligand: a cell surface molecule altered in steel mutant fibroblasts. *Cell* 63, 185-194); the specific activity of chimeric molecules was approx. 1000 U/mg. Concentrated Semaphorin-SEAP were diluted as appropriate in a HEPES buffered saline, additioned with 0.2% BSA, 0.1% NaN_3 , 5 mM CaCl_2 and 1 mM MgCl_2 (HBSBA). For binding assays, COS cells transiently transfected with plexins were seeded on 48 well plates to reach confluence, and then incubated with Semaphorin-SEAP preparations (approx 1-5 nM) for 90 minutes at room temperature. The binding was detected as described (Flanagan and Leder, 1990). Binding experiments with plexin-C1/VESPR were as described (Comeau, M.R., Johnson, R., DuBose, R.F., Petersen, M., Gearing, P., VandenBos, T., Park, L., Farrah, T., Buller, R.M., Cohen, J.I., Strockbine, L.D., Rauch, C., and Spriggs, M.K. (1998). A poxvirus-encoded semaphorin induces cytokine production from monocytes and binds to a novel cellular semaphorin receptor, VESPR. *Immunity*. 8, 473-482; He, Z. and Tessier-Lavigne, M. (1997). Neuropilin is a receptor for the axonal chemorepellent Semaphorin III. *Cell* 90, 739-751).

For *in vitro* binding assays, plexin-B1 was purified from cell extracts by immunoprecipitation with anti-VSV antibody. Extracts of mock-transfected cells were used as control samples. After washing, the immunocomplexes were incubated with serial dilutions of CD100-SEAP (prepared as above) for 2 hours at 4°C, in continuous agitation. Samples were then washed 3 times with HBSBA and the bound alkaline phosphatase activity was measured by colorimetric assay using p-nitro-phenyl-phosphate, as described (Flanagan and Leder, 1990). Scatchard analysis was done using Equilibrate (by GertJan C. Veenstra).

Example 4

In situ hybridization analysis

RNA *in situ* hybridization was performed essentially as described (He, Z. and Tessier-Lavigne, M. (1997). Neuropilin is a receptor for the axonal chemorepellent Semaphorin III. *Cell* 90, 739-751). Briefly cDNA fragments of plexin-A1, -A2, and -A3 were used to generate ³⁵S-labeled antisense and sense RNA probes, which were
5 used for in situ hybridization histochemistry of cryostat sections of rat embryos.

Example 5

Xenopus turning assay

The methods for injecting mRNA encoding various constructs, and for studying the turning responses of the neurons, are exactly as described previously (Hong, K.,
10 Hinck, L., Nishiyama, M., Poo, M.M., Tessier-Lavigne, M., and Stein, E. (1999). A ligand-gated association between cytoplasmic domains of UNC5 and DCC family receptors converts netrin-induced growth cone attraction to repulsion. *Cell* 97, 927-941); Song, H., Ming, G., He, Z., Lehmann, M., Tessier-Lavigne, M., and Poo, M. (1998). Conversion of neuronal growth cone responses from repulsion to attraction by
15 cyclic nucleotides [see comments]. *Science* 281, 1515-1518).

Example 6

Mixed-culture assays and time-lapse videomicroscopy

Mock-transfected and plexin-A3 overexpressing MDCK cells were seeded with mesenchymal cells (NIH 3T3, KJ29, D17, among others), in multiwell culture plates by
20 1:4 or 1:1 ratio. NIH and KJ-29 cells were sometimes labeled by addition of DiI (1,1'-dioctadecyl-3,3,3',3'-tetramethylindocarbocyanine perchlorate, Fluka) in the culture medium, 4 hours before harvesting for the assay; clusters of cells marked with this dye are marked in blue (in light microscopy) and emit red epifluorescence (TRITC filter). The repelling effect was observed 16-30 hours after confluency, by contrast phase
25 microscopy using Leica DM IL. The progress of the assays was also monitored by time-lapse video-microscopy (320 minutes recording were converted into 1 minute play). To determine the time-length of cell contacts, for each assay, randomly chosen fibroblasts were followed during several hours and the duration of each contact between their lamellipodia and MDCK cells was measured. The doubling time of cells and their
30 viability during the assay could also be analyzed, and no differences were observed in presence of control or plexin-A3 expressing cells. Substrate adhesion of plexin-A3 overexpressing MDCKs was analyzed by counting attached cells after 30 minutes from

seeding on micro-wells coated with fibronectin, collagen or polylysine, in the absence of calf serum: no differences versus control cells were observed.

Example 7

Apoptosis detection

5 TUNEL reaction (Boehringer detection kit) was performed on mixed cultures of MDCK and NIH3T3 cells, 24 hours after seeding in a 24-well culture plate. The labeling was converted into a colorimetric signal for analysis by light microscopy using the TUNEL-AP detection kit (Boehringer). As a positive control for the induction of apoptosis, the same cells were treated with UV-C (50 $\mu\text{J}/\text{cm}^2$) or 1 μM staurosporin.

10 Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be apparent to those skilled in the art that certain changes and modifications will be practiced. Therefore, the description and examples should not be construed as limiting the scope of the invention, which is delineated by the appended claims.

15 Example 8

Plexins are specific receptors for cell surface semaphorins in vertebrates

Plexin-C1 (VESPR) has been shown to bind the soluble viral semaphorins Sema VA and VB (Comeau et al., 1998 *supra*), and we recently found that *Drosophila* Plexin A (D Plex A) interacts with transmembrane Sema 1a (Winberg et al., 1998 *supra*). We
20 therefore examined in vertebrates whether the extracellular domain of several different cellular semaphorins -fused to alkaline phosphatase- could bind members of the human plexin-A, -B and -C subfamilies. Multiple secreted semaphorins of class 3 (Sema3A, Sema 3C or Sema3F; see below) did not interact with plexins-A1, -A2, -A3, -B1, B2, or -C1 (data not shown). In contrast, plexin-C1(Vespr) specifically bound Sema7A(Sema-
25 K1) (Fig. 2a), a GPI-membrane linked semaphorin (class 7). This result is not entirely unexpected, since Sema7A may represent the cellular counterpart of viral semaphorin SemaVB, previously shown to interact with this plexin (Comeau et al., 1998 *supra*). More interestingly, the class 4 transmembrane semaphorin Sema4D (CD100) did interact strongly and specifically with plexin-B1 (Fig. 2a). Thus the prototypes of two
30 distinct plexin families are the receptors for members of two distinct semaphorin sub-classes. We also found that Sema7A and Sema4D do not bind to neuropilin-1 or -2 alone, nor did co-transfection of either neuropilin with plexin-B1 significantly modify

its binding efficiency (not shown). Neuropilins thus seem so far to function as receptors only for vertebrate semaphorins of class 3.

The affinity constant of Sema4D for plexin-B1 was estimated by Scatchard plot to be in the subnanomolar range ($K_D = 0.9$ nM, Fig. 2b; the estimated K_D of Sema7A for plexin-C1 is 2.1 nM, not shown). These values are consistent with those observed
5 for semaphorins-neuropilins, and fly semaphorin1-Plexin A interactions (He and Tessier-Lavigne, 1997 *supra* Winberg et al., 1998).

We used two deletion constructs of plexin-B1 to explore the semaphorin binding sites of plexins. Neither the N-terminal half of plexin-B1 extracellular domain
10 ("plexin-B1 truncated", see previous paragraph), nor its C-terminal half ("plexin-B1- Δ sema", see Experimental Procedures) was sufficient alone to bind CD100 (see Fig. 2a), suggesting that the binding of Sema4D depends on multiple structural determinants of the extracellular domain of plexin-B1.

Example 9

15 Plexins associate with class 3 Semaphorin receptors, Neuropilins

As outlined above, secreted semaphorins of subclass 3 are known to bind neuropilins (He and Tessier-Lavigne, 1997 *supra*; Kolodkin et al., 1997 *supra*; Chen, H., Chedotal, A., He, Z., Goodman, C.S., and Tessier-Lavigne, M. (1997) "Neuropilin-2, a novel member of the neuropilin family, is a high affinity receptor for the
20 semaphorins Sema E and Sema IV but not Sema III." *Neuron* 19, 547-559). However, the short cytoplasmic tail of neuropilins seems to be dispensable for their biological activity (Nakamura, et al (1998) *supra*), indicating the requirement of an associated co-receptor for signal transduction. Interestingly, in *Drosophila* (where neuropilins have not been identified to date) Plexin A is sufficient to mediate the biological response to
25 semaphorin-1 in axon guidance (Winberg et al., 1998*supra*).

In an initial set of experiments, we could not observe binding of the class 3 semaphorins Sema3A(Sema III), Sema3C(Sema E) or Sema3F(Sema IV) to plexins-A1, A2, A3, B1, B2 or C1 (not shown). To test whether plexins might be coreceptors with neuropilins for class 3 semaphorins, we set up co-precipitation experiments in COS
30 cells to test whether neuropilins may interact with plexins. Three tested plexins (plexin-A1, -A3 and -B1) associated both with neuropilin-2 (Np2, shown in Fig. 3) and neuropilin-1 (not shown). The binding was specific, inasmuch as neither neuropilin nor any plexins coimmunoprecipitated with the netrin receptor DCC, under conditions

where DCC coimmunoprecipitated with the other netrin receptor UNC5H2 (Fig. 3 and data not shown). We observed finally that the plexin-neuropilin association is mediated by the *sema domain* of plexins, as demonstrated using either the "plexin-B1 truncated" splice variant (Figure 3) or an even shorter form of the extracellular domain ("plexin-B1-sema", see Experimental procedures, not shown).

To further support the idea of a plexin-neuropilin multimeric receptor complex for semaphorins, we show here that plexin-A3 (e.g.) is expressed in a large number of neuronal classes, including sensory, sympathetic, motor, and olfactory bulb neurons (Figure 4 and data not shown), which are known to respond to class 3 semaphorins, and which express either neuropilin-1 or neuropilin-2 or both (Chen et al., 1997 *supra*; Feiner, L., Koppel, A.M., Kobayashi, H., and Raper, J.A. (1997). Secreted chick semaphorins bind recombinant neuropilin with similar affinities but bind different subsets of neurons in situ. *Neuron* 19, 539-545; He and Tessier-Lavigne, 1997 *supra*; Kolodkin et al., 1997 *supra*). Thus, plexin-A3 is a candidate for a physiological coreceptor involved in mediating class 3 semaphorin effects on these axons. Other plexins may also have a role as neuropilin coreceptors in specific cell populations, such as plexin-A2, which is expressed in a subset of sensory neurons and in dorsal horn cells, and plexin-A1, which is expressed at low levels and broadly in the spinal cord (Figure 4).

To directly test the possible involvement of plexins in class 3 semaphorin signal transduction, we studied the repulsive responses of *Xenopus* spinal neurons to Sema3A, which is mediated by a receptor mechanism involving neuropilin-1 (Song et al., 1998 *supra*). We asked whether these responses could be altered by expression of a presumed dominant-negative plexin-A1 construct lacking the cytoplasmic domain of the protein. Transmembrane proteins can be reliably expressed in these neurons by injecting the encoding mRNA at the developmental two cell stage, allowing the embryos to grow to tadpole stage, and then removing the spinal cord and culturing the neurons (Hong et al., 1999 *supra*). We therefore injected the mRNA encoding the truncated plexin-A1 construct, together with mRNA encoding GFP (as a reporter) and then studied the responses of spinal neurons expressing GFP that were derived from these embryos. Whereas control spinal neurons are repelled by Sema3A (Figure 5A, B and Song et al. 1998 *supra*), neurons from embryos injected with mRNA for truncated plexin-A1 did not respond with either repulsion or attraction to Sema3A (Figure 5C,

D). This blocking effect appeared to be specific, since expression of a different heterologous receptor, UNC5H2, did not impair repulsion by *Sema3A* (Hong et al., 1997 *supra*), and since expression of the truncated plexin construct did not block attractive responses to netrin-1 (Figure 5E, F). Figure 5G, H quantifies these effects. As can be seen, the effect of *Sema3A* is completely abolished by the truncated plexin; although there is a slight apparent decrease in the attractive effect of netrin-1 the effect is not statistically significant.

Although we have used a truncated plexin-A1 construct, this construct may be expected to interfere with the function of various plexins, since all the plexins tested (A1, A3 and B1) associated with neuropilin-1. These results support a role for one or more plexins in mediating the repulsive *Sema3A* signal in the *Xenopus* spinal neurons.

Example 10

Plexins signal via a novel type of tyrosine phosphorylated cytoplasmic domain

The sequences of plexin cytoplasmic domains are highly conserved among plexins but do not match any known sequences. We found that the plexin-A3 and plexin-B1 proteins are phosphorylated on tyrosine residues when overexpressed in human kidney cells (BOSC-23), as demonstrated using anti-phosphotyrosine antibodies (Fig. 6a). Furthermore, after immunoprecipitation and in vitro kinase assays, plexin-A3 and plexin-B1 became phosphorylated (Fig. 6b). Resistance to an alkali treatment (see Experimental procedures) confirmed the specific phosphorylation of tyrosine residues.

The cytoplasmic domains of several receptors, including Met proteins, become tyrosine phosphorylated owing to an intrinsic kinase activity (Ullrich, A. and Schlessinger, J. (1990) "Signal transduction by receptors with tyrosine kinase activity." *Cell* 61, 203-212). Since the cytoplasmic domain of plexins is not similar to any bona fide or atypical tyrosine kinase, this suggests that a distinct tyrosine kinase co-immunoprecipitates in association with plexins, and is responsible for their tyrosine phosphorylation. Although some additional phosphorylated proteins can be found specifically with plexin-A3 and -B1, we have not as yet identified this associated kinase. A number of endogenously expressed tyrosine kinases, namely Met, Ron, Abl and Src, were not found associated with plexin-A3 by immunoprecipitation and Western blotting (not shown). Since tyrosine phosphorylated residues often function as docking sites for intracellular signal transducers (Cantley, L.C., Auger, K.R., Carpenter, C., Duckworth, B., Graziani, A., Kapeller, R., and Soltoff, S. (1991) "Oncogenes and

signal transduction." Cell 64, 281-302), the fact that the cytoplasmic domains of plexins are tyrosine phosphorylated further suggests that they are part of signaling complexes.

Example 11

5 Plexin-A3 expressing cells induce repulsion of co-cultured cells

Stable transfectants expressing recombinant human plexin-A3 were successfully obtained in four different cell lines: IMR32 and AF8 (human neuroblasts), and BOSC-23 and MDCK (human and canine kidney cells, respectively). We observed modest phenotypic changes in the transfected cells, which generally become flatter and larger in size. The growth rate of plexin-A3 overexpressing cells was comparable to parental lines and we did not observe differences in the ability to adhere on different substrates (data not shown).

In keeping with previous report on the related Plexin of *Xenopus laevis* (Ohta, K., Mizutani, A., Kawakami, A., Murakami, Y., Kasuya, Y., Takagi, S., Tanaka, H.,
15 and Fujisawa, H. (1995). "Plexin: a novel neuronal cell surface molecule that mediates cell adhesion via a homophilic binding mechanism in the presence of calcium ions." Neuron 14, 1189-1199), we observed a modest increase in calcium-dependent homotypic cell aggregation of plexin-A3 transfectants (not shown). Surprisingly, we found that epithelial MDCK cells overexpressing plexin-A3 mediate strong repelling
20 cues for adjacent cells. This was observed by co-culturing mock-transfected and plexin-A3 overexpressing MDCK cells together with several non-epithelial cell lines (such as NIH3T3, KJ29, and D17; Fig. 7A). Mock MDCKs grew alongside mesenchymal cells until confluency, when both cell types stopped proliferating. In contrast, when plexin-A3-overexpressing epithelial cells were grown in the same conditions, the adjacent
25 mesenchymal cells withdrew from them, and ultimately detached from the plate.

To analyze the dynamics of this repulsion process, we monitored for 36 hours, by time-lapse video-microscopy, mixed cultures of transfected MDCK cells and fibroblasts, in a number of independent experiments. At low cell density, fibroblasts showed intrinsic motility, exploring the surface of the plate with long lamellipodia and
30 filopodia, and thus coming in contacts with a high number of stationary MDCK islets. The time-length of the contacts between fibroblasts and control MDCK cells varied from 30 minutes to several hours, lasting mostly over 100 minutes. However, when fibroblasts were cultured with MDCK cells overexpressing plexin-A3, transient

contacts were observed, often lasting less than 30 minutes (see Fig. 7C). At higher cell density, fibroblasts stopped and clustered alongside the islands of control MDCKs, whereas they kept moving in a hectic fashion between the islands of plexin-A3 transfected cells (data not shown).

5 This cell-repelling effect is not due to the release of soluble factors, since exchanging conditioned media between mixed cultures was without effect (not shown). Moreover, the two different cell populations grew normally until they came into contact, indicating that the repelling effect requires cell-cell interaction. To rule out the possibility that plexin-A3 expressing cells generate an apoptotic signal for fibroblasts,
10 we monitored cell viability and apoptosis by TUNEL staining. As shown in Figure 7B, the clusters of repelled fibroblasts did not include apoptotic cells; furthermore, the detaching cells still excluded Trypan blue stain and were able to spread again on a new culture plate (not shown).

 Taken together, these results demonstrate that in our experimental system, plexin-
15 A3 mediates cell repelling cues, presumably by interacting with surface bound ligands on opposing cells. We could not identify –so far– the specific ligand for plexin-A3, however we propose that this may be a transmembrane semaphorin. It should be noted that the intracellular domains of transmembrane semaphorins, such as Sema4D, also
20 include tyrosine residues, which may themselves become phosphorylated and associate with cytoplasmic signal transducer molecules, a property shown for ligands of the ephrin family (Holland, S.J., Gale, N.W., Mbamalu, G., Yancopoulos, G.D., Henkemeyer, M., and Pawson, T. (1996) "Bidirectional signalling through the EPH-family receptor Nuk and its transmembrane ligands." *Nature* 383, 722-725).

What is claimed is:

- 5 1. Isolated nucleic acid having at least 80% nucleic acid sequence identity to a nucleotide sequence that encodes an amino acid sequence selected from the group consisting of the amino acid sequence shown in (SEQ ID NO: 2 (plexin B-2)), (SEQ ID NO: 4 (plexin B-3)), (SEQ ID NO: 6 (plexin D-1)) and (SEQ ID NO: 8 (plexin A-4))
- 10 2. Isolated nucleic acid having at least 80% nucleic acid sequence identity to a nucleotide sequence selected from the group consisting of the nucleotide sequence shown (SEQ ID NO: 1 (plexin B-2)), (SEQ ID NO: 3 (plexin B-3)), (SEQ ID NO: 5 (plexin D-1)) and (SEQ ID NO: 7 (plexin A-4)).
3. A vector comprising the nucleic acid of any one of claims 1 or 2.
- 15 4. An isolated polypeptide having at least 80% amino acid sequence identity to an amino acid sequence selected from the group consisting of the amino acid sequence shown in (SEQ ID NO: 2 (plexin B-2)), (SEQ ID NO: 4 (plexin B-3)), (SEQ ID NO: 6 (plexin D-1)) and (SEQ ID NO: 8 (plexin A-4)).
5. An isolated polypeptide having at least 80% amino acid sequence identity to:
 - 20 (a) the polypeptide shown in (SEQ ID NO: 2 (plexin B-2)), (SEQ ID NO: 4 (plexin B-3)), (SEQ ID NO: 6 (plexin D-1)) and (SEQ ID NO: 8 (plexin A-4)), lacking its associated signal peptide;
 - (b) an extracellular domain of the polypeptide shown in (SEQ ID NO: 2 (plexin B-2)), (SEQ ID NO: 4 (plexin B-3)), (SEQ ID NO: 6 (plexin D-1)) and (SEQ ID NO: 8 (plexin A-4)), with its associated signal peptide; or
 - 25 (c) an extracellular domain of the polypeptide shown in (SEQ ID NO: 2 (plexin B-2)), (SEQ ID NO: 4 (plexin B-3)), (SEQ ID NO: 6 (plexin D-1)) and (SEQ ID NO: 8 (plexin A-4)), lacking its associated signal peptide.

6. A chimeric molecule comprising a polypeptide according to claim 4 or 5 fused to a heterologous amino acid sequence.
7. The chimeric molecule of claim 6, wherein the heterologous amino acid sequence is a Fc region of an immunoglobulin.
- 5 8. An antibody that specifically binds to a polypeptide according to claim 4 or 5.
9. The antibody according to claim 8, wherein the antibody is a monoclonal, a humanized antibody or a single-chain antibody.
- 10 10. A method of suppressing or altering aberrant cell growth involving a signaling pathway between a plexin and a neuropilin in a mammal comprising the step of administering an effective amount of an agent to said mammal capable of interfering with the association between the plexin and neuropilin.
- 15 11. A method of treating, suppressing or altering a disorder involving aberrant immune regulation involving a signaling pathway between a plexin and a neuropilin in a mammal comprising the step of administering an effective amount of an agent to said mammal capable of interfering with the association between the plexin and neuropilin.
- 20 12. The method according to claim 10 or 11 wherein said agent is a chimeric molecule according to claim 6 or 7.
13. The method according to claim 10 or 11, wherein said agent is an antibody according to claim 8 or 9.
- 25 14. A method of diagnosing or screening for tumors in a subject characterized by the expression profiles of the polypeptides according to claim 4 or 5 wherein the expression profile of the polypeptides is different in a non-tumor sample as compared to the expression profile of the polypeptides in a tumor sample.

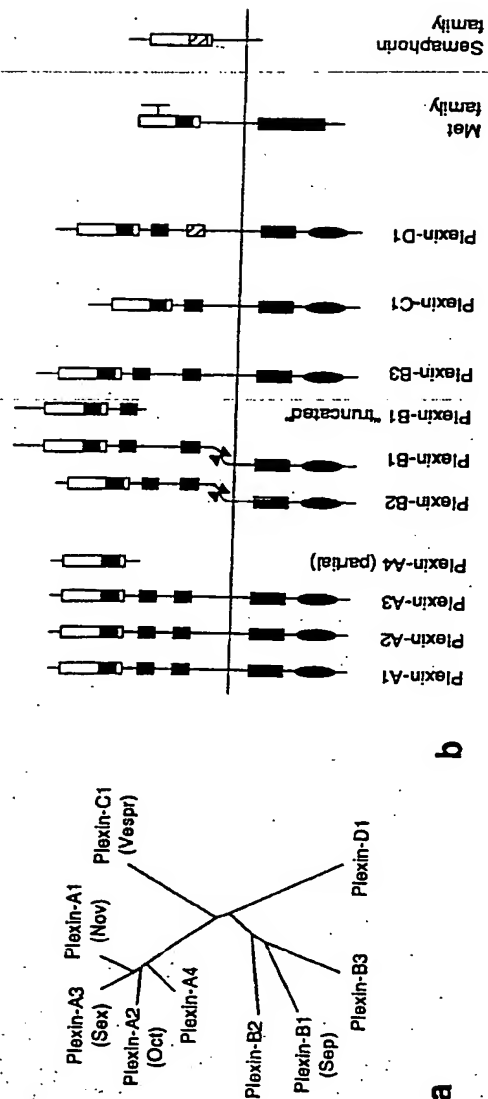
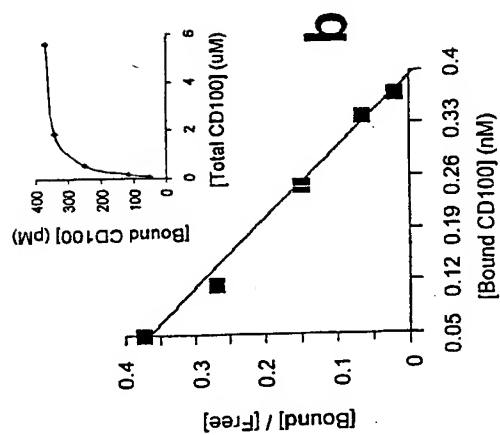
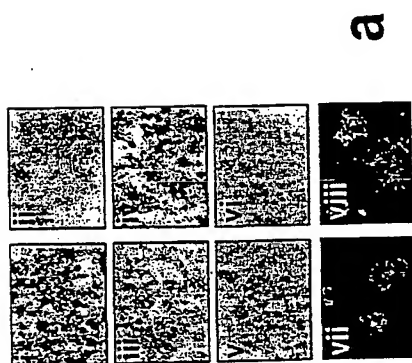
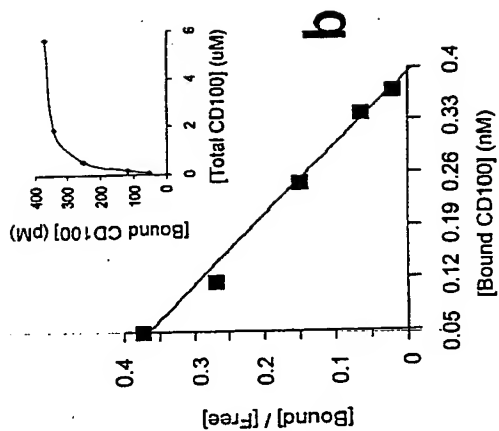
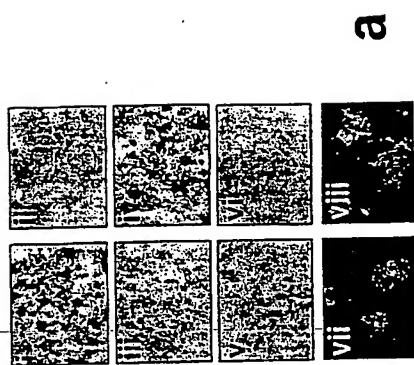


Figure 1 (Tamagnone et al.)



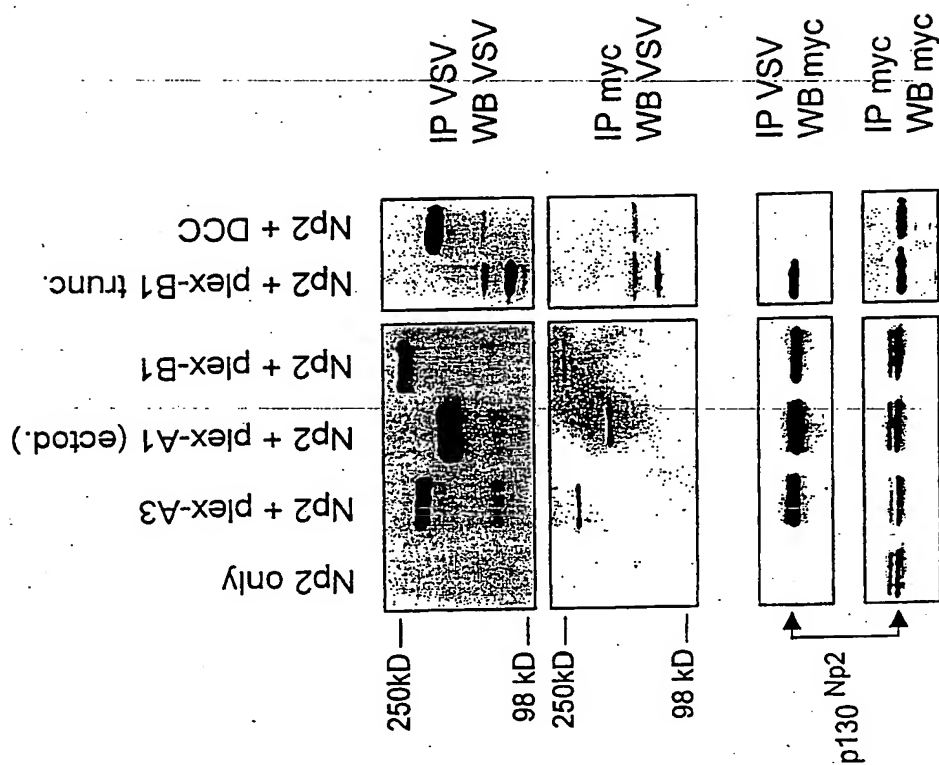
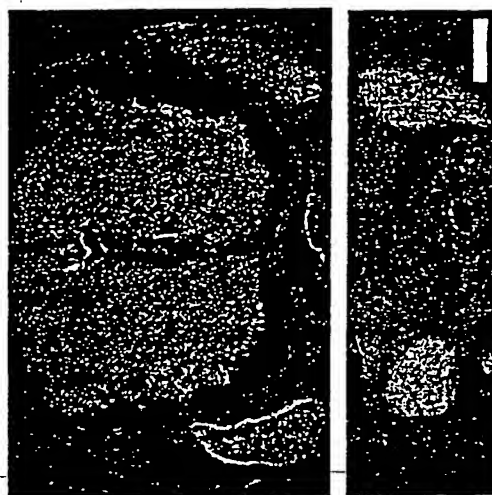
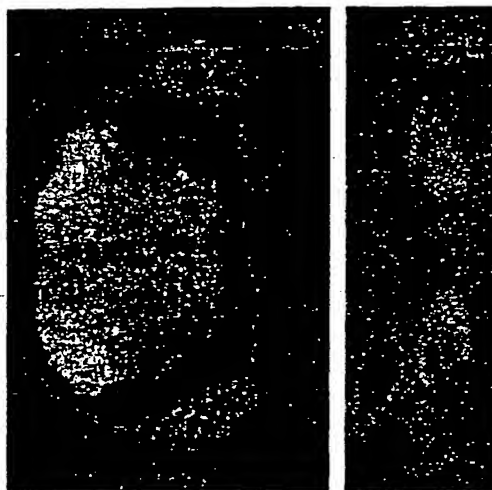


FIG. 3

Plexin-A3



Plexin-A2



Plexin-A1

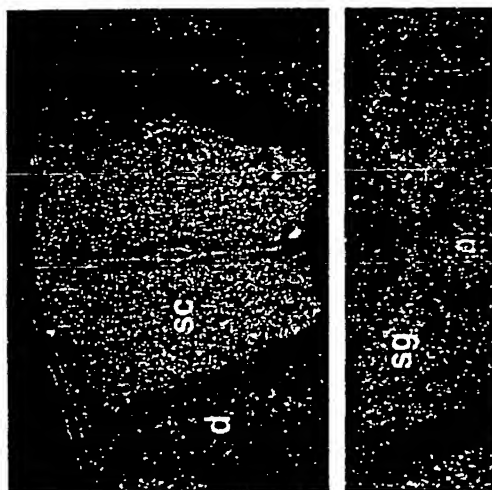


FIG. 4

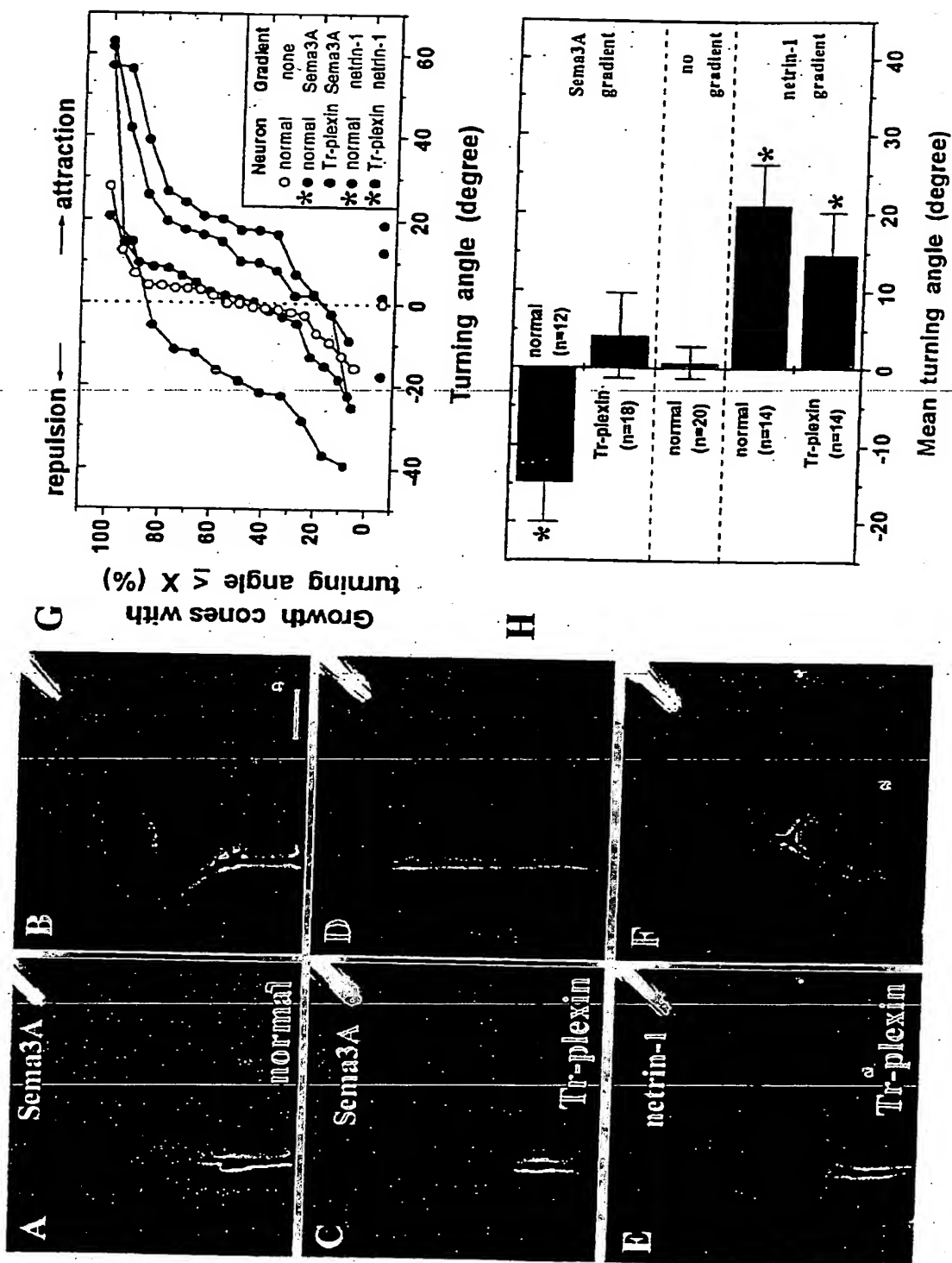


FIG. 5

6/7

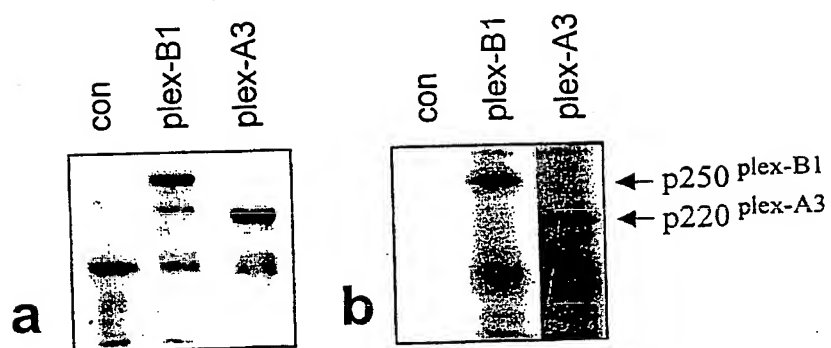
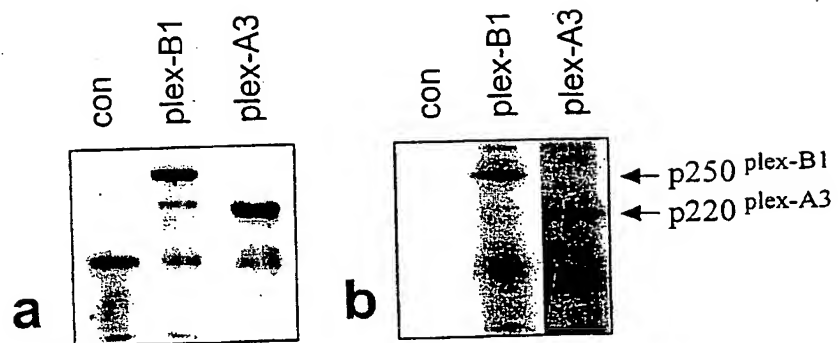
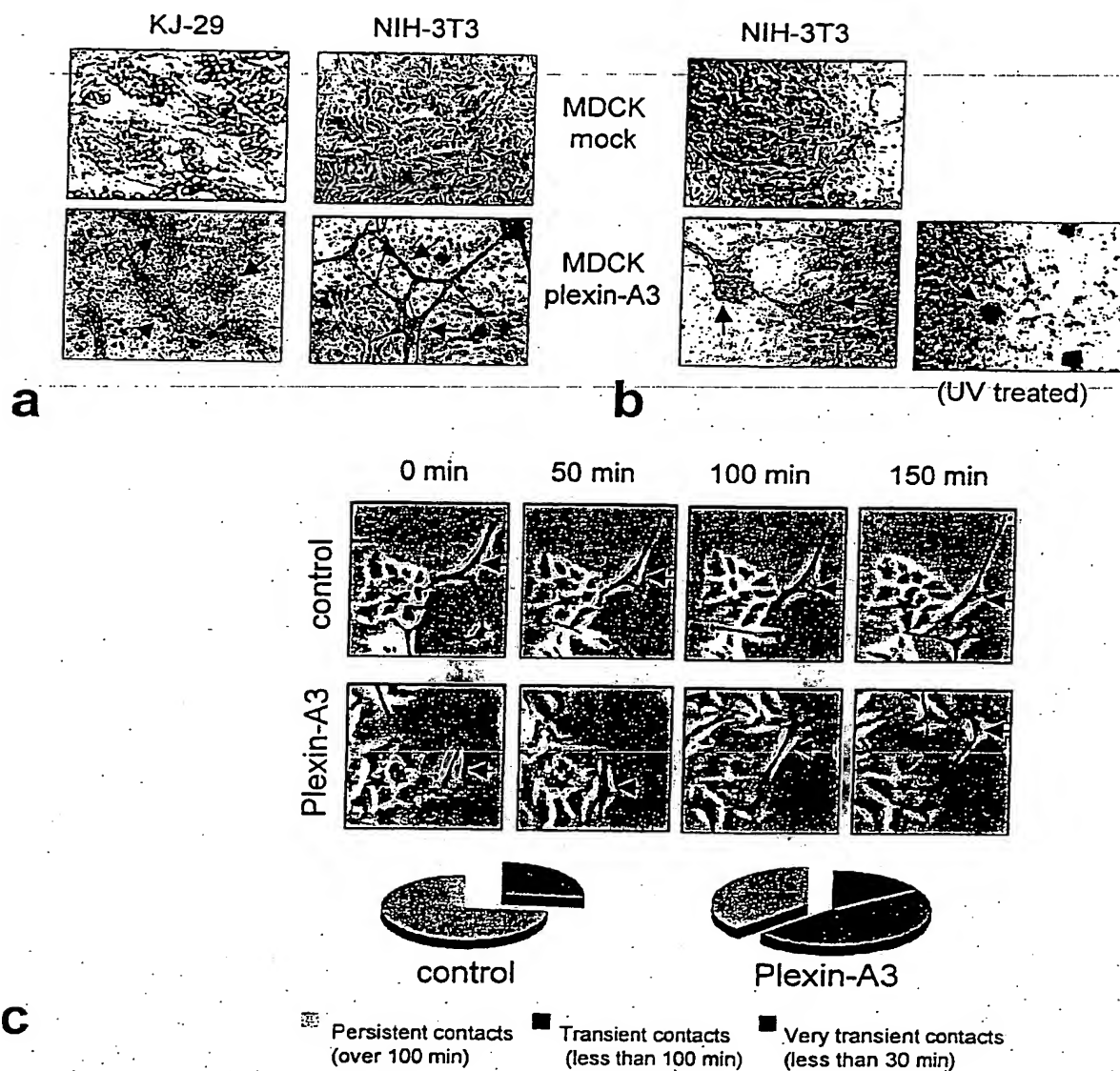


Fig. 6

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FIG. 7



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Ser	Leu	Ile	Gln	Arg	Phe	Ala	Met	Val	Val	Ile	Ala	Glu	Pro	Leu	Gln	1010	1015	1020
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Ser	Pro	Ala	Val	Pro	Glu	Glu	Pro	Glu	Ala	Tyr	Asn	Leu	Thr	Val	Leu	1060	1065	1070
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Gln Val Lys Glu	Lys Ile Ile Asp Gln Val Tyr Arg Gly	Gln Pro Cys
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Gln Ile Gln Asp Met Thr Pro Leu Ser Glu Gln Glu Met Asn Ala His
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 Ala Met Ala Glu Ile Phe Arg Ser Pro Lys Arg Tyr Arg Pro Gln Ile
 1875 1880 1885
 Met Ala Ala Leu Glu Ala Asn Pro Thr Ala Arg Arg Thr Gln Leu Gln
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 Phe Ala Ser Glu Met Lys Gln Cys Val Arg Leu Thr Val His Pro Asn
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 65 70 75 80
 Asn Val Pro Glu Leu Ser Ala Gly Val Asn Cys Thr Phe Glu Asp Leu
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 Ser Glu Met Asp Gly Leu Val Val Gly Asn Gln Ile Gln Cys Tyr Ser
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 Pro Ala Ala Lys Glu Val Pro Arg Ile Ile Thr Glu Asn Gly Asp His
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 His Val Val Gln Leu Gln Leu Lys Ser Lys Glu Thr Gly Met Thr Phe
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Ala Ser Thr Ser Phe Val Phe Tyr Asn Cys Ser Val His Asn Ser Cys
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<400> 10

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Pro	Pro	Ala	Asp	Pro	Gly	Pro	Glu	Ala	Leu	His	Pro	Thr	Val	Pro	Leu				
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Asp	Leu	Pro	Pro	Ala	Thr	Val	Pro	Ala	Thr	Thr	Phe	Pro	Gly	Ala	Met				
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Gly	Ser	Val	Lys	Pro	Ala	Leu	Asp	Trp	Leu	Thr	Arg	Glu	Gly	Gly	Glu				
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Leu	Pro	Glu	Ala	Asp	Glu	Trp	Thr	Gly	Gly	Asp	Ala	Pro	Ala	Phe	Ser				
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Thr	Ser	Thr	Leu	Leu	Ser	Gly	Asp	Gly	Asp	Ser	Ala	Glu	Leu	Glu	Gly				
865					870					875					880				
Pro	Pro	Ala	Pro	Leu	Ile	Leu	Pro	Ser	Ser	Leu	Asp	Tyr	Gln	Tyr	Asp				
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Thr	Pro	Gly	Leu	Trp	Glu	Leu	Glu	Glu	Ala	Thr	Leu	Gly	Ala	Ser	Ser				
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Cys	Pro	Cys	Val	Glu	Ser	Val	Gln	Gly	Ser	Thr	Leu	Met	Pro	Val	His				
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Val	Glu	Arg	Glu	Ile	Arg	Leu	Leu	Gly	Arg	Asn	Leu	His	Leu	Phe	Gln				
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Asp	Gly	Pro	Gly	Asp	Asn	Glu	Cys	Val	Met	Glu	Leu	Glu	Gly	Leu	Glu				
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Val	Val	Val	Glu	Ala	Arg	Val	Glu	Cys	Glu	Pro	Pro	Pro	Asp	Thr	Gln				
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Cys	His	Val	Thr	Cys	Gln	Gln	His	Gln	Leu	Ser	Tyr	Glu	Ala	Leu	Gln				
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Pro	Glu	Leu	Arg	Val	Gly	Leu	Phe	Leu	Arg	Arg	Ala	Gly	Arg	Leu	Arg				
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Val	Asp	Ser	Ala	Glu	Gly	Leu	His	Val	Val	Leu	Tyr	Asp	Cys	Ser	Val				
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Cys	Val	Trp	Cys	Glu	Gly	Glu	Arg	Pro	Arg	Cys	Val	Thr	Arg	Glu	Ala				
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Cys	Gly	Glu	Ala	Glu	Ala	Val	Ala	Thr	Gln	Cys	Pro	Ala	Pro	Leu	Ile				
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His	Ser	Val	Glu	Pro	Leu	Thr	Gly	Pro	Val	Asp	Gly	Gly	Thr	Arg	Val				
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Met	Val	Thr	Val	Ala	Gly	Val	Pro	Cys	Ala	Val	Asp	Ala	Gln	Glu	Tyr				
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 Ser Lys Leu Leu Thr Gly Arg Leu Glu Asp Ile Arg Val Val Val Gly
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 Trp Phe Gly Ala Thr Glu Arg Arg Leu Gln Arg Gly Gln Phe Lys Tyr
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 Arg His Lys Pro Gly Ser Val Phe Ser Val Glu Gly Glu Asn Leu Asp
 1395 1400 1405
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Gln Gly Leu Gly	Gln Leu Ser Asn Leu	Leu Asn Ser Lys Leu	Phe Leu			
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Thr Lys Phe Ile His Thr	Leu Glu Ser Gln Arg Thr	Phe Ser Ala Arg				
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Asp Arg Ala Tyr Val Ala	Ser Leu Thr Val Ala	Leu His Gly Lys				
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Leu Glu Tyr Phe Thr Asp	Ile Leu Arg Thr Leu	Leu Ser Asp Leu Val				
	1650	1655	1660			
Ala Gln Tyr Val Ala Lys	Asn Pro Lys Leu Met	Leu Arg Arg Thr Glu				
	1665	1670	1675			
Thr Val Val Glu Lys Leu	Leu Thr Asn Trp Met	Ser Ile Cys Leu Tyr				
	1685	1690	1695			
Thr Phe Val Arg Asp Ser	Val Gly Glu Pro Leu	Tyr Met Leu Phe Arg				
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Gly Ile Lys His Gln Val	Asp Lys Gly Pro Val	Asp Ser Val Thr Gly				
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Lys Ala Lys Tyr Thr Leu	Asn Asp Asn Arg Leu	Leu Arg Glu Asp Val				
	1730	1735	1740			
Glu Tyr Arg Pro Leu Thr	Leu Asn Ala Leu Leu	Ala Val Gly Pro Gly				
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Ala Gly Glu Ala Gln Gly	Val Pro Val Lys Val	Leu Asp Cys Asp Thr				
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Ile Ser Gln Ala Lys Glu	Lys Met Leu Asp Gln	Leu Tyr Lys Gly Val				
	1780	1785	1790			
Pro Leu Thr Gln Arg Pro	Asp Pro Arg Thr Leu	Asp Val Glu Trp Arg				
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Ser Gly Val Ala Gly His	Leu Ile Leu Ser Asp	Glu Asp Val Thr Ser				
	1810	1815	1820			
Glu Val Gln Gly Leu Trp	Arg Arg Leu Asn Thr	Leu Gln His Tyr Lys				
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Val Pro Asp Gly Ala Thr	Val Ala Leu Val Pro	Cys Leu Thr Lys His				
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Val Leu Arg Glu Asn Gln	Asp Tyr Val Pro Gly	Glu Arg Thr Pro Met				
	1860	1865	1870			
Leu Glu Asp Val Asp Glu	Gly Gly Ile Arg Pro	Trp His Leu Val Lys				
	1875	1880	1885			
Pro Ser Asp Glu Pro Glu	Pro Pro Arg Pro Arg	Arg Gly Ser Leu Arg				
	1890	1895	1900			
Gly Gly Glu Arg Glu Arg	Ala Lys Ala Ile Pro	Glu Ile Tyr Leu Thr				
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Arg Leu Leu Ser Met Lys	Gly Thr Leu Gln Lys	Phe Val Asp Asp Leu				
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Phe Gln Val Ile Leu Ser	Thr Ser Arg Pro Val	Pro Leu Ala Val Lys				
	1940	1945	1950			
Tyr Phe Phe Asp Leu Leu	Asp Glu Gln Ala Gln	Gln His Gly Ile Ser				
	1955	1960	1965			
Asp Gln Asp Thr Ile His	Ile Trp Lys Thr Asn	Ser Leu Pro Leu Arg				
	1970	1975	1980			
Phe Trp Ile Asn Ile Ile	Lys Asn Pro Gln Phe	Val Phe Asp Val Gln				
	1985	1990	1995			
Thr Ser Asp Asn Met Asp	Ala Val Leu Leu Val	Ile Ala Gln Thr Phe				
	2005	2010	2015			
Met Asp Ala Cys Thr Leu	Ala Asp His Lys Leu	Gly Arg Asp Ser Pro				
	2020	2025	2030			

Ile Asn Lys Leu Leu Tyr Ala Arg Asp Ile Pro Arg Tyr Lys Arg Met
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 2050 2055 2060
 Gln Glu Met Asn Ser Val Leu Ala Glu Leu Ser Trp Asn Tyr Ser Gly
 2065 2070 2075 2080
 Asp Leu Gly Ala Arg Val Ala Leu His Glu Leu Tyr Lys Tyr Ile Asn
 2085 2090 2095
 Lys Tyr Tyr Asp Gln Ile Ile Thr Ala Leu Glu Glu Asp Gly Thr Ala
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 <213> HOMO SAPIEN

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<400> 12

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Thr	Tyr	Leu	Gln	His	Leu	Ala	Arg	Asp	Pro	Thr	Ser	Gly	Thr	Leu	Tyr
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Glu	Ala	Thr	Val	Ser	Thr	Gly	Pro	Val	Leu	Asp	Ser	Arg	Asp	Cys	Leu
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Pro	Pro	Val	Met	Pro	Asp	Glu	Cys	Pro	Gln	Ala	Gln	Pro	Thr	Asn	Asn
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Pro	Asn	Gln	Leu	Leu	Val	Ser	Pro	Gly	Ala	Leu	Val	Val	Cys	Gly	
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Ser	Val	His	Gln	Gly	Val	Cys	Glu	Gln	Arg	Arg	Leu	Gly	Gln	Leu	Glu
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Gln	Leu	Leu	Leu	Arg	Pro	Glu	Arg	Pro	Gly	Asp	Thr	Gln	Tyr	Val	Ala
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Ala	Asn	Asp	Pro	Ala	Val	Ser	Thr	Val	Gly	Leu	Val	Ala	Gln	Gly	Leu
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Ala	Gly	Glu	Pro	Leu	Phe	Val	Gly	Arg	Gly	Tyr	Thr	Ser	Arg	Gly	
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Val	Gly	Gly	Gly	Ile	Pro	Pro	Ile	Thr	Thr	Arg	Ala	Leu	Trp	Pro	Pro
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Asp	Pro	Gln	Ala	Ala	Phe	Ser	Tyr	Glu	Glu	Thr	Ala	Lys	Leu	Ala	Val
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Gly	Arg	Leu	Ser	Glu	Tyr	Ser	His	His	Phe	Val	Ser	Ala	Phe	Ala	Arg
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Gly	Ala	Ser	Ala	Tyr	Phe	Leu	Phe	Leu	Arg	Arg	Asp	Leu	Gln	Ala	Gln
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Ser	Arg	Ala	Phe	Arg	Ala	Tyr	Val	Ser	Arg	Val	Cys	Leu	Arg	Asp	Gln
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His	Tyr	Tyr	Ser	Tyr	Val	Glu	Leu	Pro	Leu	Ala	Cys	Glu	Gly	Gly	Arg
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Tyr	Gly	Leu	Ile	Gln	Ala	Ala	Ala	Val	Ala	Thr	Ser	Arg	Glu	Val	Ala
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His	Gly	Glu	Val	Leu	Phe	Ala	Ala	Phe	Ser	Ser	Ala	Ala	Pro	Pro	Thr
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Val	Gly	Arg	Pro	Pro	Ser	Ala	Ala	Ala	Gly	Ala	Ser	Gly	Ala	Ser	Ala
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Leu	Cys	Ala	Phe	Pro	Leu	Asp	Glu	Val	Asp	Arg	Leu	Ala	Asn	Arg	Thr
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Arg	Asp	Ala	Cys	Tyr	Thr	Arg	Glu	Gly	Arg	Ala	Glu	Asp	Gly	Thr	Glu
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Val	Ala	Tyr	Ile	Glu	Tyr	Asp	Val	Asn	Ser	Asp	Cys	Ala	Gln	Leu	Pro

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Val Asp Thr Leu Asp Ala Tyr Pro Cys Gly Ser Asp His Thr Pro Ser		
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Pro Met Ala Ser Arg Val Pro Leu Glu Ala Thr Pro Ile Leu Glu Trp		
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Pro Gly Ile Gln Leu Thr Ala Val Ala Val Thr Met Glu Asp Gly His		
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Thr Ile Ala Phe Leu Gly Asp Ser Gln Gly Gln Leu His Arg Val Tyr		
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Leu Gly Pro Gly Ser Asp Gly His Pro Tyr Ser Thr Gln Ser Ile Gln		
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Gln Gly Ser Ala Val Ser Arg Asp Leu Thr Phe Asp Gly Thr Phe Glu		
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His Leu Tyr Val Met Thr Gln Ser Thr Leu Leu Lys Val Pro Val Ala		
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Ser Cys Ala Gln His Leu Asp Cys Ala Ser Cys Leu Ala His Arg Asp		
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Pro Tyr Cys Gly Trp Cys Val Leu Leu Gly Arg Cys Ser Arg Arg Ser		
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Glu Cys Ser Arg Gly Gln Gly Pro Glu Gln Trp Leu Trp Ser Phe Gln		
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Pro Glu Leu Gly Cys Leu Gln Val Ala Ala Met Ser Pro Ala Asn Ile		
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Ser Arg Glu Glu Thr Arg Glu Val Phe Leu Ser Val Pro Asp Leu Pro		
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Pro Leu Trp Pro Gly Glu Ser Tyr Ser Cys His Phe Gly Glu His Gln		
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Ser Pro Ala Leu Thr Gly Ser Gly Val Met Cys Pro Ser Pro Asp		
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Pro Ser Glu Ala Pro Val Leu Pro Arg Gly Ala Asp Tyr Val Ser Val		
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Ser Val Glu Leu Arg Phe Gly Ala Val Val Ile Ala Lys Thr Ser Leu		
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Ser Phe Tyr Asp Cys Val Ala Val Thr Glu Leu Arg Pro Ser Ala Gln		
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Cys Gln Ala Cys Val Ser Ser Arg Trp Gly Cys Asn Trp Cys Val Trp		
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Gln His Leu Cys Thr His Lys Ala Ser Cys Asp Ala Gly Pro Met Val		
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Ala Ser His Gln Val Met Glu Thr Gln Gln Ser Leu Arg Ala Leu Pro		
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Pro Pro Ser Ser Ser Arg Pro Ala Ser Thr Thr Ser Met Thr Pro Pro		
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Gly Ser Gly Ser Trp Lys Arg Arg Pro Trp Gly Gln Ala Pro Ala Pro		
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Val Trp Arg Ala Phe Arg Ala Pro Arg		
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